Petition/Pet.1
520

Patent Term Extension Application
for U. S. Patent No. 5,002,953

#17

"EXPRESS MAIL CERTIFICATE"
"EXPRESS MAIL" MAILING LABEL NUMBER EL175490787US
DATE OF DEPOSIT July 21, 1999
I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE COMMISSIONER OF PATENTS AND TRADEMARKS, WASHINGTON, D.C. 20231.
NAME OF PERSON MAILING PAPER OR FEE
(TYPE OR PRINT) [illegible]
SIGNATURE [signature]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,002,953 July 21, 1999

Issued: March 26, 1991

To: Richard M. Hindley

For: COMPOUNDS

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

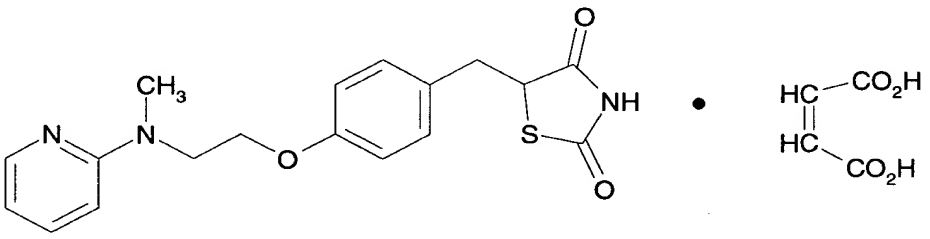
Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

The Applicant, Beecham Group, p.l.c., a corporation organized under the laws of England, having a principal place of business at Four New Horizons Court, Brentford, Middlesex TW8 9EP, England, represents that it is the assignee of the entire right, title, and interest in and to United States Letters Patent No. 5,002,953 granted to the inventor Richard M. Hindley on March 26, 1991 by virtue of an Assignment from said inventor to Applicant, executed July 6, 1993 and recorded in the United States Patent and Trademark Office on July 9, 1993 at Reel 6710, Frame 0340.

The Applicant hereby requests an extension of the term of U. S. Patent No. 5,002,953 under 35 U.S.C. §156. The information required by 37 C.F.R. §1.740 is set forth below:

1. The approved product is **AVANDIA®**. The generic name of the approved product is rosiglitazone maleate. The chemical name of the approved product is (±)-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]-phenyl]methyl]-2,4-thiazolidinedione, (*Z*)-2-butenedioate (1:1). The approved product has the following chemical structure:



rosiglitazone maleate

2. The approved product was subject to regulatory review under Section 505 of the Federal Food, Drug and Cosmetic Act, (Act of June 25, 1938, c.675, §505, 52 Stat. 1052, as amended; herein after "FFDC Act"), codified at 21 U.S.C. §355.

3. The United States Food and Drug Administration (herein after "FDA") approved **AVANDIA®** for commercial marketing and use under the FFDC Act on May 25, 1999.

4. The active ingredient in the approved product is rosiglitazone maleate, having the chemical name and structure described in 1., *supra*. The active ingredient has never been previously approved for commercial marketing or use under the FFDC Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

5. This application for extension of patent term is being submitted within the sixty day period allowed by law for such submission in accordance with the requirements of 35 U.S.C. §156(d)(1) and 37 C.F.R. §1.720(f), the last day of such period being July 24, 1999.

6. The complete identification of the patent for which extension is being sought is as follows:

Patent Number: 5,002,953
Earliest U.S. Filing Date: August 30, 1988
Issue Date: March 26, 1991
Date of Expiration: August 30, 2008
Inventor: Richard M. Hindley
For: COMPOUNDS

7. A copy of U. S. Patent No. 5,002,953, for which extension is being sought, is attached herewith as "Attachment A".

8. Copies of the Maintenance Fee Statement from the United States Patent and Trademark Office listing the date of payment of the fourth year and eighth year maintenance fees for U. S. Patent No. 5,002,953 are attached as "Attachment B".

9. U. S. Patent No. 5,002,953 claims the approved product as identified in paragraph 1, *supra*. Claims 1-4, 7-12, 42, and 49-55 read on the approved product. In particular, Claims 1-4, 7-12, and 49-51 are directed to genera of compounds which include the active ingredient. Claim 42 is directed specifically to the active ingredient identified in paragraph 4, *supra*. Claim 52 is directed to a generic pharmaceutical composition comprising a compound of Claim 1, including the active ingredient. Claims 53-55 are directed to methods of treatment of hyperglycemia and hyperlipidemia comprising administering a compound of Claim 1, including the active ingredient.

10. In accordance with 35 U.S.C. §156(g), listed below are the relevant dates and information to enable the Secretary of Health and Human Services to determine the applicable regulatory review period:

a. The effective date of the investigational new drug ("IND") application for **AVANDIA®** was October 22, 1993. The IND was assigned number 43,468;

b. The new drug application ("NDA") for **AVANDIA®** was submitted on November 24, 1998. The NDA was assigned number 21-071; and

c. NDA 21-071 for **AVANDIA®** was approved on May 25, 1999.

11. A brief description of the significant activities undertaken by the Applicant during the applicable regulatory review period with respect to **AVANDIA®** and the significant dates applicable to such activities is attached hereto as "Attachment C".

12. Applicant is of the opinion that U. S. Patent No. 5,002,953 is eligible for extension under 35 U.S.C. §156. The length of extension of the term of U. S. Patent No. 5,002,953 claimed by Applicant is 1,021 days or about two years and ten months. More specifically:

(a) the regulatory review period under 35 U.S.C. §156(g)(1)(B) was from October 22, 1993 until May 25, 1999, such period being 2,041 days or about five years and seven months. The regulatory review period is the sum of:

(1) the period for review under 35 U.S.C. §156(g)(1)(B)(i), which was from October 22, 1993 (the effective date of IND 43,468) until November 24, 1998 (date of submission of NDA 21-071), such period being 1,859 days or about five years and two months; and

(2) the period for review under 35 U.S.C. §156(g)(1)(B)(ii), which was from November 24, 1998 (date of submission of NDA 21-071) until May 25, 1999 (date of approval of NDA 21-071), such period being 182 days or about six months;

(b) under 35 U.S.C. §156(c)(2), in the absence of other statutory limitations, the permitted period of extension calculated according 37 C.F.R. §1.775(c) and (d)(1) would have been:

(i) the regulatory review period, which is the sum of:
(A) the 35 U.S.C. §156(g)(1)(B)(i) period of 1,859 days or about five years and two months; and
(B) the 35 U.S.C. §156(g)(1)(B)(ii) period of 182 days, or about five months;
totaling 2,041 days or about five years and seven months;

(ii) from which is subtracted:
(A) the number of days in the regulatory review period which occurred on or before the date of issue of U. S. Patent No. 5,002,953, that is, from October 22, 1993 (the effective date of IND 43,468) until March 26, 1991 (the date of issue of U. S. Patent No. 5,002,953), being 0 days; and
(B) one-half the number of days remaining after the 35 U.S.C. §156(g)(1)(B)(i) period defined in 12(b)(i)(A) *supra* is reduced by the period defined in 12(b)(ii)(A) *supra*, being 1020 days or about two years and five months;
totaling 1,021 days or about two years and ten months.

(c) under 35 U.S.C. §156(g)(6)(A), the permitted period of extension determined on the basis of the regulatory review period may not exceed five years. As shown in paragraph 12(b), *supra*, the permitted period of extension under 35 U.S.C. §156(c)(2) is 1,021 days or about two years and ten months, and therefore does not exceed the five year maximum;

(d) U. S. Patent No. 5,002,953 was in force on June 8, 1995. In accordance with 35 U.S.C. §154(c)(1), the term of such patent is the greater of 20 years from the earliest date on which the application for patent was filed in the United States or seventeen years from date of grant. The term of U. S. Patent No. 5,002,953 calculated 20 years from the date on which the application for patent was filed, August 30, 1988, expires on August 30, 2008. The term of U. S. Patent No. 5,002,953 calculated 17 years from the date of grant, March 26, 1991, expires March 26, 2008. Therefore, the normal expiration date of U. S. Patent No. 5,002,953 is August 30, 2008.

(e) under 35 U.S.C. §156(c)(3) the period remaining in the term of the patent to be extended after the date of approval of the approved product, when added to the permitted period of extension, may not exceed fourteen years.

The period remaining in the term of U. S. Patent No. 5,002,953 after the date of approval of the approved product (3,385 days or about nine years and five months), when added to the permitted period of extension calculated in 12(b), *supra* (1,021 days or about two years and ten months) is 4,406 days or about twelve years and one month. Fourteen years from the date of approval of the approved product, ending on May 25, 2013, is 5,114 days. Thus, the permitted period of extension under 35 U.S.C. §156(c)(2) does not exceed the fourteen year cap under 35 U.S.C. §156(c)(3). Therefore, the period of extension to which Applicant is entitled is 1,021 days or about two years and ten months.

(f) Applicant hereby requests that the term of U. S. Patent No. 5,002,953 be extended by 1,021 days from the date of normal patent expiration;

(g) Patents issued before the June 8, 1995 effective date of the Uruguay Round Agreements Act are entitled to add patent term extension under 35 U.S.C. §156 to the twenty years-from-filing patent term under 35 U.S.C. §154(c)(1). *Merck & Co. v. Kessler* 38 USPQ2d 1347 (Fed. Cir. 1996). Therefore, the expiration date of U. S. Patent No. 5,002,953, extended in accordance with this application, would be June 17, 2011.

13. Applicant and the undersigned acknowledge a duty under 37 C.F.R. §1.740(a)(13) to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to any determination to be made relative to this application for extension.

14. The prescribed fee under 37 C.F.R. §1.20(j), of One Thousand One Hundred Twenty Dollars ($1,120.00) for filing this application is to be charged to Applicant's Deposit Account 19-2570 as authorized in the accompanying letter, which is submitted herewith in duplicate.

15. Please direct all inquiries and correspondence relating to this application to:

Yuriy P. Stercho, Ph.D.
SmithKline Beecham Corporation
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939
Telephone: (610) 270-5018
Facsimile: (610) 270-5090

16. A duplicate of this application, certified as such, is submitted herewith.

17. Attached hereto is a Declaration, which meets the criteria set forth in under 37 C.F.R. §1.740(b), signed on behalf of Beecham Group, p.l.c.

Respectfully submitted,
BEECHAM GROUP, P.L.C.

By: 

Yuriy P. Stercho, Ph.D.
Attorney for Applicant
Registration No. 33,797

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In re: U.S. Patent No. 5,002,953 July 21, 1999

Issued: March 26, 1991

To: Richard M. Hindley

For: COMPOUNDS

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

DECLARATION

Sir:

The undersigned attorney for Beecham Group, p.l.c., which is the applicant for extension of patent term under 35 U.S.C. § 156 with respect to U.S. Patent No. 5,002,953 declares:

(1) That he is an attorney registered to practice before the United States Patent and Trademark Office and that he has general authority from the owner of U.S. Patent No. 5,002,953 to act on behalf of the owner in patent matters as authorized by the attached Power of Attorney;

(2) That he has reviewed and understands the contents of the application being submitted pursuant to 35 U.S.C. § 156 and the guidelines for extension of patent term under 37 CFR § 1.740;

(3) That he believes the patent is subject to extension pursuant to 35 U.S.C. § 156 and the regulations therefor under 37 CFR § 1.710;

(4) That he believes an extension of the length claimed is fully justified under 35 U.S.C. § 156 and the applicable regulations; and

(5) That he believes the patent for which the extension is being sought meets the requirements for extension of the term of a patent as set forth in 35 U.S.C. § 156 and the regulations therefor under 37 CFR § 1.720.

The undersigned hereby declares further that all statements made herein of his own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any extension of patent term issuing thereon.

Date: July 21, 1999

By: _____
Yuriy P. Stercho, Ph.D.
Attorney for Applicant
Registration No. 33,797

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COPY

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Issued: March 26, 1991

To: Richard M. Hindley

For: COMPOUNDS

July 21, 1999

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

POWER OF ATTORNEY

Sir:

Beecham Group p.l.c., a corporation organized under the laws of England, having a principal place of business at Four New Horizons Court, Brentford, Middlesex TW8 9EP, England, hereby authorizes Yuriy P. Stercho, a patent attorney registered to practice before the U.S. Patent and Trademark Office, Registration No. 33,797, whose business address is SmithKline Beecham Corporation, Corporate Intellectual Property - U.S., 709 Swedeland Road, King of Prussia, PA 19406-0939, to act in the name of and on behalf of Beecham Group, p.l.c., with full power of substitution and revocation, to transact all business in the United States Patent and Trademark Office connected with the above-identified patent, including the power to apply for patent term extension in the name of and on behalf of Beecham Group, p.l.c..

Please address all future correspondence and telephone calls as follows:

Yuriy P. Stercho, Ph.D.
SmithKline Beecham Corporation
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939
Telephone: (610) 270-5018
Facsimile: (610) 270-5090

Dated: July 21, 1999

BEECHAM GROUP, P.L.C.

By: _____

Name: Stephen Venetianer
Title: Vice President, Pharmaceuticals

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Thus the correct extended expiration date of the above-identified patent is September 16, 2011.

Applicants have enclosed corrected substitute pages 6 and 7 of the Application for the Examiner's convenience.

Respectfully submitted,
BEECHAM GROUP, P.L.C.

By: _____

Yuriy P. Stercho, Ph.D.
Attorney for Applicant
Registration No. 33,797

SmithKline Beecham Corporation
Corporate Intellectual Property - UW2220
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Telephone: (610) 270-5018
Facsimile: (610) 270-5090

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12. Applicant is of the opinion that U. S. Patent No. 5,002,953 is eligible for extension under 35 U.S.C. §156. The length of extension of the term of U. S. Patent No. 5,002,953 claimed by Applicant is 1,112 days or about three years. More specifically:

(a) the regulatory review period under 35 U.S.C. §156(g)(1)(B) was from October 22, 1993 until May 25, 1999, such period being 2,041 days or about five years and seven months. The regulatory review period is the sum of:

(1) the period for review under 35 U.S.C. §156(g)(1)(B)(i), which was from October 22, 1993 (the effective date of IND 43,468) until November 24, 1998 (date of submission of NDA 21-071), such period being 1,859 days or about five years and two months; and

(2) the period for review under 35 U.S.C. §156(g)(1)(B)(ii), which was from November 24, 1998 (date of submission of NDA 21-071) until May 25, 1999 (date of approval of NDA 21-071), such period being 182 days or about six months;

(b) under 35 U.S.C. §156(c)(2), in the absence of other statutory limitations, the permitted period of extension calculated according 37 C.F.R. §1.775(c) and (d)(1) would have been:

(i) the regulatory review period, which is the sum of:

(A) the 35 U.S.C. §156(g)(1)(B)(i) period of 1,859 days or about five years and two months; and

(B) the 35 U.S.C. §156(g)(1)(B)(ii) period of 182 days, or about six months;

totaling 2,041 days or about five years and eight months;

(ii) from which is subtracted:

(A) the number of days in the regulatory review period which occurred on or before the date of issue of U. S. Patent No. 5,002,953, that is, from October 22, 1993 (the effective date of IND 43,468) until March 26, 1991 (the date of issue of U. S. Patent No. 5,002,953), being 0 days; and

(B) one-half the number of days remaining after the 35 U.S.C. §156(g)(1)(B)(i) period defined in 12(b)(i)(A) *supra* is reduced by the period defined in 12(b)(ii)(A) *supra*, being 929 days or about two years and six months;

totaling 1,112 days or about three years.

(c) under 35 U.S.C. §156(g)(6)(A), the permitted period of extension determined on the basis of the regulatory review period may not exceed five years. As shown in paragraph 12(b), *supra*, the permitted period of extension under 35 U.S.C. §156(c)(2) is 1,112 days or about three years, and therefore does not exceed the five year maximum;

(d) U. S. Patent No. 5,002,953 was in force on June 8, 1995. In accordance with 35 U.S.C. §154(c)(1), the term of such patent is the greater of 20 years from the earliest date on which the application for patent was filed in the United States or seventeen years from date of grant. The term of U. S. Patent No. 5,002,953 calculated 20 years from the date on which the application for patent was filed, August 30, 1988, expires on August 30, 2008. The term of U. S. Patent No. 5,002,953 calculated 17 years from the date of grant, March 26, 1991, expires March 26, 2008. Therefore, the normal expiration date of U. S. Patent No. 5,002,953 is August 30, 2008.

(e) under 35 U.S.C. §156(c)(3) the period remaining in the term of the patent to be extended after the date of approval of the approved product, when added to the permitted period of extension, may not exceed fourteen years.

The period remaining in the term of U. S. Patent No. 5,002,953 after the date of approval of the approved product (3,385 days or about nine years and five months), when added to the permitted period of extension calculated in 12(b), *supra* (1,112 days or about three years) is 4,497 days or about twelve years and four months. Fourteen years from the date of approval of the approved product, ending on May 25, 2013, is 5,114 days. Thus, the permitted period of extension under 35 U.S.C. §156(c)(2) does not exceed the fourteen year cap under 35 U.S.C. §156(c)(3). Therefore, the period of extension to which Applicant is entitled is 1,112 days or about three years.

(f) Applicant hereby requests that the term of U. S. Patent No. 5,002,953 be extended by 1,112 days from the date of normal patent expiration;

(g) Patents issued before the June 8, 1995 effective date of the Uruguay Round Agreements Act are entitled to add patent term extension under 35 U.S.C. §156 to the twenty years-from-filing patent term under 35 U.S.C. §154(c)(1). *Merck & Co. v. Kessler* 38 USPQ2d 1347 (Fed. Cir. 1996). Therefore, the expiration date of U. S. Patent No. 5,002,953, extended in accordance with this application, would be September 16, 2011.

POWER OF ATTORNEY

The undersigned Beecham Group p.l.c., formerly Beecham Group Limited, a corporation of England hereby authorizes in the name and on behalf of Beecham Group p.l.c., Stephen Venetianer, a patent attorney registered with the U.S. Patent and Trademark Office, Registration No. 25,659 whose business address is SmithKline Beecham Corporation, Corporate Patents - U.S., UW2220, P.O. Box 1539, King of Prussia, Pa. 19406-0939, USA to act on behalf of Beecham Group p.l.c. in all patent matters including the power to execute (or revoke) powers of attorney, disclaimers, patent term extensions, concessions of priority, abandonments, assents to filing reissue applications, petitions to make special, applications to correct inventorship, patent assignments, pleadings, interrogatories, oppositions, affidavits of use, and petitions for reexamination, and to execute all other papers and take all such actions as he may deem necessary or appropriate in order to file, prosecute, abandon, terminate, extend or transfer applications for patents and other industrial property rights in the United States and countries foreign thereto, and to defend, assert, and maintain such property rights in full force and effect.

Executed as of the 22 day of January, 1992.

BEECHAM GROUP p.l.c.

David Roberts
Director and Senior Vice President
Corporate Patents

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For: COMPOUNDS

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

CERTIFICATION

The undersigned hereby certifies that the attached photocopy is an exact duplicate of the application for extension of patent term of U.S. Patent No. 5,002,953 under 35 U.S.C. §1.56, including its attachments and supporting papers, mailed to the U.S. Patent and Trademark Office on this date.

Date: July 21, 1999 By: _____
Yuriy P. Stercho, Ph.D.
Attorney for Applicant
Registration No. 33,797

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COPY

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In re: U.S. Patent No. 5,002,953 July 21, 1999

Issued: March 26, 1991

To: Richard M. Hindley

For: COMPOUNDS

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Re: Deposit Account No. 19-2570
SmithKline Beecham Corporation
U.S. Patent No. 5,002,953

Sir:

Transmitted herewith is an original application under 35 U.S.C. § 156 for extension of the term of U.S. Patent No. 5,002,953. One photocopy of the original application is submitted herewith.

Please charge Deposit Account No. 19-2570 in the amount of $1,120.00. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Deposit Account No. 19-2570. A duplicate copy of this sheet is enclosed.

Respectfully submitted,
BEECHAM GROUP, P.L.C.

By: _____

Yuriy P. Stercho, Ph.D.
Attorney for Applicant
Registration No. 33,797

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ATTACHMENT A

United States Patent [19]

Hindley

[11] **Patent Number: 5,002,953**

[45] **Date of Patent: Mar. 26, 1991**

[54] **COMPOUNDS**

[75] Inventor: **Richard M. Hindley, Surrey, England**

[73] Assignee: **Beecham Group p.l.c., Brentford, England**

[21] Appl. No.: **457,272**

[22] Filed: **Dec. 27, 1989**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 238,764, Aug. 30, 1988, abandoned.

[30] **Foreign Application Priority Data**

Sep. 4, 1987 [GB] United Kingdom 8720825
Nov. 30, 1987 [GB] United Kingdom 8727987
Feb. 4, 1988 [GB] United Kingdom 8802454

[51] Int. Cl.[5] **C07D 417/12**; A61K 31/125; A61K 31/44; A61K 31/55

[52] U.S. Cl. **514/275**; 514/342; 514/367; 514/359; 544/332; 546/280; 548/161; 548/181; 548/183

[58] Field of Search 548/182, 181, 161; 546/280; 544/332; 514/369, 367, 342, 275

[56] **References Cited**

FOREIGN PATENT DOCUMENTS

008203 2/1980 European Pat. Off. .

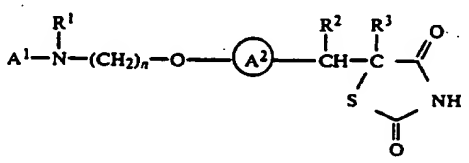
OTHER PUBLICATIONS

Chemical and Pharmaceutical Bulletin, vol. 30, No. 10, Oct. 1982, pp. 3580–3600, Tokyo, JP; T. Sohda et al. "Studies on Antidiabetic Agents, (II.1) Synthesis of 5–[4–(1–methylcyclohexylmethoxy)–benzyl]-thiazolidine–2,4–dione (ADD–3878) and its Derivatives", pp. 3585–3588, 3590, 3591*.

Primary Examiner—Robert Gerstl
Attorney, Agent, or Firm—Hopgood, Calimafde, Kalil, Blaustein & Judlowe

[57] **ABSTRACT**

Compounds of formula (I):



(I)

or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;

R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

R^2 and R^3 each represent hydrogen, or R^2 and R^3 together represent a bond;

A^2 represents a benzene ring having in total up to five substituents; and

n represents an integer in the range of from 2 to 6; pharmaceutical compositions containing such compounds and the use of such compounds and compositions in medicine.

55 Claims, No Drawings

NOVEL COMPOUNDS

This application is a continuation-in-part of U.S. Ser. No. 238,764, filed Aug. 30, 1988, now abandoned.

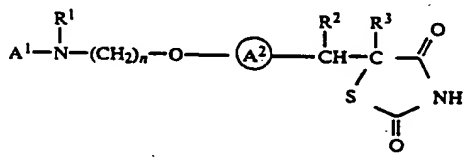
This invention relates to certain substituted thiazolidinedione derivatives, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

European Patent Applications, Publication Numbers 0008203, 0139421, 0155845, 0177353, 0193256, 0207581 and 0208420 relate to thiazolidinedione derivatives which are disclosed as having hypoglycaemic and hypolipidaemic activity. Chem. Pharm. Bull 30 (10) 3580–3600 also relates to certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic activities.

It has now surprisingly been discovered that certain novel substituted-thiazolidinedione derivatives show improved blood-glucose lowering activity and are therefore of potential use in the treatment and/or prophylaxis of hyperglycaemia and are of particular use in the treatment of Type II diabetes.

These compounds are also indicated to be of potential use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders.

Accordingly, the present invention provides a compound of formula (I):



(I)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;

R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

R^2 and R^3 each represent hydrogen, or R^2 and R^3 together represent a bond;

A^2 represents a benzene ring having in total up to five substituents; and

n represents an integer in the range of from 2 to 6.

Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

Favoured aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 4 to 7 ring atoms, preferably 5 or 6 ring atoms.

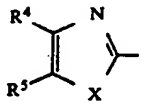
In particular, the aromatic heterocyclyl group comprises 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

Suitable values for A^1 when it represents a 5- membered aromatic heterocyclyl group include thiazolyl and oxazolyl, especially oxazolyl.

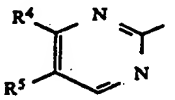
Suitable values for A^1 when it represents a 6- membered aromatic heterocyclyl group include pyridyl or pyrimidinyl.

Suitably R^2 and R^3 each represent hydrogen.

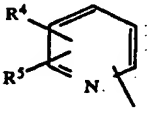
Preferably, A^1 represents a moiety of formula (a), (b) or (c):



(a)



(b)



(c)

wherein:

R^4 and R^5 each independently represents a hydrogen atom, an alkyl group or a substituted or unsubstituted aryl group or when R^4 and R^5 are each attached to adjacent carbon atoms, then R^4 and R^5 together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R^4 and R^5 together may be substituted or unsubstituted; and in the moiety of formula (a)

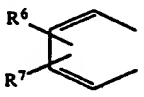
X represents oxygen or sulphur.

Aptly, A^1 represents a moiety of the abovedefined formula (a).

Aptly, A^1 represents a moiety of the abovedefined formula (b).

Aptly. A^1 represents a moiety of the abovedefined formula (c).

In one favoured aspect R^4 and R^5 together represent a moiety of formula (d):



(d)

wherein R^6 and R^7 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

Suitably, R^6 and R^7 each independently represent hydrogen, halogen, alkyl or alkoxy.

Favourably, R^6 represents hydrogen. Favourably, R^7represents hydrogen.

Preferably, R^6 and R^7 both represent hydrogen.

In a further favoured aspect R^4 and R^5 each independently represent hydrogen, alkyl or a substituted or unsubstituted phenyl group and more favourably, R^4 and R^5 each independently represent hydrogen, alkyl or phenyl.

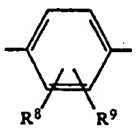
Preferably, for the moiety of formula (a), R^4 and R^5 together represent the moiety of formula (d).

Preferably, for the moieties of formula (b) or (c), R^4 and R^5 both represent hydrogen.

It will be appreciated that the five substituents of A^2 include three optional substituents. Suitable optional

substituents for the moiety A^2 include halogen, substituted or unsubstituted alkyl or alkoxy.

Favourably, A^2 represents a moiety of formula (e):



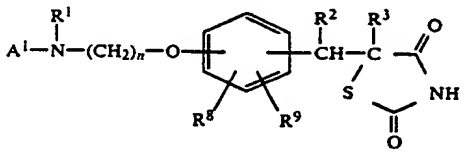
(e)

wherein R^8 and R^9 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

Suitably, R^8 and R^9 each independently represent hydrogen, halogen, alkyl or alkoxy. Preferably, R^8 and R^9 each represent hydrogen.

Favourably, X represents oxygen. Favourably, X represents sulphur.

In one preferred aspect the present invention provides a class of compounds, which fall wholly within the scope of formula (I), of formula (II):



(II)

or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein A^1, R^1, R^2, R^3, and n are as defined in relation to formula (I) and R^8 and R^9 are as defined in relation to formula (e).

Suitably, n represents an integer 2, 3 or 4, notably 2 or 3 and especially 2.

Suitably, R^1 represents hydrogen, alkyl, acyl, especially acetyl, or benzyl.

When R^1 represents an alkyl group, examples of such alkyl groups include methyl and isopropyl. Preferably, R^1 represents a methyl group.

As indicated above a compound of formula (I) may exist in one of several tautomeric forms, all of which are encompassed by the present invention. It will be appreciated that the present invention encompasses all of the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof, including any stereoisomeric forms thereof, whether as individual isomers or as mixtures of isomers.

Suitable substituents for any heterocyclyl group include up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

When used herein the term 'aryl' includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine; preferably chlorine.

When used herein the terms 'alkyl' and 'alkoxy' relate to groups having straight or branched carbon chains, containing up to 12 carbon atoms.

When used herein the term 'acyl' includes alkylcarbonyl groups. Suitable alkyl groups are C_1–C_{12} alkyl groups, especially C_1–C_6 alkyl groups e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

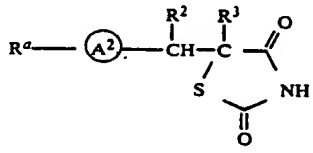
Suitable pharmaceutically acceptable salts include salts of the thiazolidinedione moiety, and, where appropriate, salts of carboxy groups.

Suitable pharmaceutically acceptable salts of the thiazolidinedione moiety include metal salts especially alkali metal salts such as the lithium, sodium and potassium salts.

Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example aluminium, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine or quinoline.

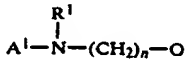
Suitable pharmaceutically acceptable solvates include hydrates.

In a further aspect the present invention also provides a process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, which process comprises reacting a compound of formula (III):



(III)

wherein R^2, R^3 and A^2 are as defined in relation to formula (I), and R^a is a moiety convertible to a moiety of formula (f):



(f)

wherein R^1, A^1, and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^a to the said moiety (f) and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) to a further compound of formula (I);

(ii) preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

Suitably, R^a represents R^1HN-$(CH_2)n$—O—wherein R^1 and n are as defined in relation to formula (I).

Suitably, when R^a is R^1HN-$(CH_2)n$—O—, an appropriate reagent capable of converting R^a to a moiety (f) is a compound of formula (IV):

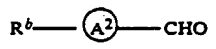
$$A^1-R^x \quad (IV)$$

wherein A^1 is as defined in relation to formula (I) and R^x represents a leaving group.

A suitable leaving group R^x includes a halogen atom, preferably a chlorine or bromine atom, or a thioalkyl group for example a thiomethyl group.

The reaction between the compound of formula (III) and the appropriate reagent may be carried out under conditions suitable to the particular compound of formula (III) and the reagent chosen; thus for example the abovementioned reaction between a compound of formula (III) wherein R^a represents R^1HN-$(CH_2)n$—O— and the compound of formula (IV), may be carried out in any suitable solvent, for example tetrahydrofuran, at a temperature in the range of between 0° and 60° C.

A compound of formula (III) may be prepared from a compound of formula (V):



(V)

wherein A^2 is as defined in relation to the compound of formula (I) and R^b is a moiety R^a, or a moiety convertible to a moiety R^a; by reaction of the compound of formula (V) with 2,4-thiazolidinedione; and thereafter if required carrying out one or more of the following optional steps:

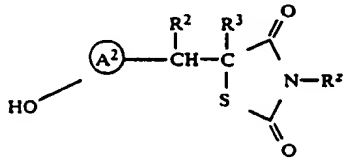
(i) reducing a compound of formula (III) wherein R^2 and R^3 together represent a bond, into a compound of formula (III) wherein R^2 and R^3 each represent hydrogen;

(ii) converting a moiety R^b to a moiety R^a.

The reaction between the compound of formula (V) and 2,4-thiazolidinedione will of course be carried out under conditions suitable to the nature of the compound of formula (V), in general the reaction being carried out in a solvent such as toluene, suitably at an elevated temperature such as the reflux temperature of the solvent and preferably in the presence of a suitable catalyst such as piperidinium acetate or benzoate. Favourably, in the reaction between the compound of formula (V) and 2,4-thiazolidinedione, the water produced in the reaction is removed from the reaction mixture, for example by means of a Dean and Stark apparatus.

When R^a represents R^1HN-$(CH_2)n$—O—, a suitable value for R^b is a hydroxyl group.

The moiety R^b may be converted to the moiety R^a by any suitable means, for example when R^b represents a hydroxyl group and R^a represents $RIHN(CH_2)n$—O— the appropriate conversion may be carried out by coupling a compound of formula (VA):



(VA)

wherein R^2, R^3 and A^2 are as defined in relation to formula (I) and R^z is hydrogen or a nitrogen protecting group, with a compound of formula (VI):

$$R^1NR^z(CH_2)_n—OH \quad (VI)$$

wherein R^1 and n are as defined in relation to formula (I) and R^z is hydrogen or a nitrogen protecting group, in the presence of a suitable coupling agent; and thereafter, if required, carrying out one or more of the following optional steps:

(i) reducing a compound of formula (III) wherein R^2 and R^3 together represent a bond, to a compound of formula (III) wherein R^2 and R^3 each represent hydrogen;

(ii) removing any nitrogen protecting group.

A suitable coupling agent for the coupling reaction between the compound of formula (VA) and (VI) is provided by diethylazodicarboxylate and triphenylphosphine. The coupling reaction may be carried out in any suitable solvent at a low to medium temperature, for example in tetrahydrofuran at a temperature in the range of between 0° and 60° C.

One example of the preparation of a compound of formula (VA) is that wherein a compound falling within formula

(v) of particular formula (VII):

(VII)

wherein A^2 is as defined in relation to formula (I), and R^{11} represents a hydroxyl group or a protected hydroxyl group, is reacted with 2,4-thiazolidinedione; and thereafter if required removing any protecting group.

Preferably, R^{11} represents a benzyloxy group.

Suitable conditions for the reaction between a compound of formula (VII) and 2,4-thiazolidinedione are those defined above in relation to the reaction between the compounds of formula (V) and 2,4-thiazolidinedione.

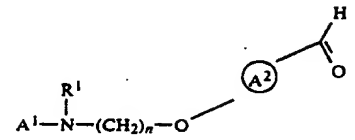
The compounds of formula (IV), (VI) and (VII) are either known compounds or are prepared using methods analogous to those used to prepare known compounds.

Suitable protecting groups in any of the abovementioned reactions are those used conventionally in the art. Thus, for example, a suitable nitrogen protecting group is a benzyl group or a benzyloxycarbonyl group and a suitable hydroxyl protecting group is a benzyl group.

The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example when R^{11} represents a benzyloxy group such group may be prepared by treatment of the appropriate compound of formula (VII), wherein R^{11} is a hydroxyl group with a benzyl halide, such as benzyl bromide, and thereafter when required the benzyl group may be conveniently removed using a mild ether cleavage reagent such as trimethylsilyliodide.

A compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate

thereof, may also be prepared by reacting a compound of formula (VIII):



(VIII)

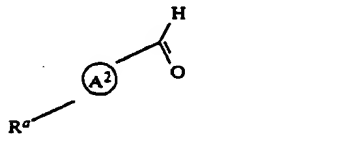
wherein R^1, A^1, A^2, and n are as defined in relation to formula (I) with 2,4-thiazolidinedione; and thereafter if required carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

The reaction between a compound of formula (VIII) and 2,4-thiazolidinedione may suitably be carried out under analogous conditions to those used in the reaction between a compound of formula (V) and 2,4-thiazolidinedione.

A compound of formula (VIII) may be prepared by reacting a compound of formula (IX):



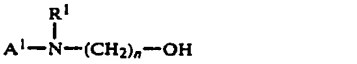
(IX)

wherein A^2 is as defined in relation to formula (I) and R^a is as defined in relation to formula (III), with an appropriate reagent capable of converting R^a to the above defined moiety (f).

Suitable values for R^a include those described above in relation to the compound of formula (III). Thus R^a may represent R^1HN-(CH_2)n—O—, as defined above, and hence the appropriate compound of formula (IX) may be reacted with a reagent of the abovedefined formula (IV) to provide the required compound of formula (VIII).

Suitable reaction conditions for the reaction of the compound of formula (IX) and the appropriate reagent may include those described above in relation to the preparation of compound (III) with the said appropriate reagent.

Preferably, for the compound of formula (IX), R^a represents a leaving group, especially a fluorine atom. When R^a represents a leaving group, preferably a fluorine atom, a particularly appropriate reagent is a compound of formula (X):



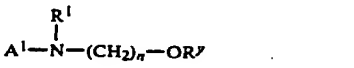
(X)

wherein R^1, A^1, and n are as defined in relation to formula (I).

The reaction between the compounds of formulae (IX) and (X) may be carried out under any suitable conditions, for example in a solvent such as dimethylformamide or dimethylsulphoxide at an elevated temperature for example in the range of between 100° to 150° C., suitably in the presence of a base such as sodium hydride or potassium carbonate.

In the compound of formula (IX) R^a may also represent a hydroxyl group.

When R^a, in the compound of formula (IX), represents a hydroxyl group a particularly appropriate reagent is a compound of the above defined formula (X) or a compound of formula (XA):



(XA)

wherein A^1, R^1 and n are as defined in relation to formula (X) and R^y represents a tosylate or mesylate group.

The reaction between the compound of formula (IX) wherein R^a is a hydroxyl group and the reagent of the abovedefined formula (X) may suitably be carried out in an aprotic solvent, such as tetrahydrofuran, at low to medium temperature, for example at ambient temperature, and preferably in the presence of a coupling agent such as that provided by triphenylphosphine and diethylazodicarboxylate.

The reaction between the compound of formula (IX), wherein R^a is a hydroxyl group, and the reagent of the abovedefined formula (XA) may be carried out in an aprotic solvent, such as dimethylformamide, at a low to elevated temperature, for example in the range of from 50° C. to 120° C. and preferably in the presence of a base, such as sodium hydride.

The compound of formula (XA) may be prepared from the corresponding compound of formula (X) by reaction with either a tosyl halide or a mesyl halide in a solvent such as pyridine.

The compounds of formula (IX) are known compounds or compounds prepared by methods analogous to those used to prepare known compounds, for example 4-fluorobenzaldehyde and 4-hydroxybenzaldehyde are known commercially available compounds.

The reagent of formula (X) may be prepared by reacting a compound of the hereinabove defined formula (IV), with a compound of the hereinbefore defined formula (VI) and thereafter if required removing any nitrogen protecting group using the appropriate conventional conditions.

The reaction between the compounds of formula (IV) and (VI) may be carried out under any suitable conditions, such as in solvent, for example in an aprotic solvent such as tetrahydrofuran, at a low to medium temperature, for example a temperature in the range of from 0° to 60° C.

Favourably when R^1 represents hydrogen the reaction is carried out using the compound of formula (VI) as a solvent at a low to elevated temperature, suitably an elevated temperature such as in the range of between 100° and 170° C.

The abovementioned conversion of a compound of formula (I) into a further compound of formula (I) includes the following conversions:

(a) reducing a compound of formula (I) wherein R^2 and R^3 together represent a bond, to a compound of formula (I) wherein R^2 and R^3 each represent hydrogen; and

(b) converting one group R^1 into another group R^1.

The conversion of a compound of formula (I) to a further compound of formula (I) may be carried out by using any appropriate conventional procedure.

A suitable reduction method for the abovementioned conversion (a) includes catalytic reduction or the use of a metal/solvent reducing system.

Suitable catalysts for use in the catalytic reduction are palladium on carbon catalysts, preferably a 10% palladium on charcoal catalyst; the reduction being carried out in a solvent, for example dioxan, suitably at ambient temperature.

Suitable metal/solvent reducing systems include magnesium in methanol.

The abovementioned reduction of a compound of formula (III) wherein R^2 and R^3 together represent a bond to a compound of formula (III) wherein R^2 and R^3 each represent hydrogen, may be carried out under analogous conditions to those referred to above in conversion (a) of the compound of formula (I).

In the abovementioned conversion (b), suitable conversions of one group R^1 into another group R^1 includes converting a group R^1 which represents hydrogen into a group R^1 which represents an acyl group.

The conversion of a compound of formula (I) wherein R^1 represents hydrogen into a compound of formula (I) wherein R^1 represents acyl may be carried out using any appropriate conventional acylation procedure, such as by treating an appropriately protected compound of formula (I) with an acylating agent. For example acetic anhydride may be used to prepare the compound of formula (I) wherein R^1 is acetyl.

It will be appreciated that in the abovementioned conversions (a) and (b), any reactive group in the compound of formula (I) would be protected, according to conventional chemical practice, where necessary.

Where appropriate the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof may be prepared as individual isomers using conventional chemical procedures.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties:

The present invention accordingly provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

Thus the present invention provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia.

In a further aspect the present invention also provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of hyperlipidaemia.

As indicated hereinbefore the present invention also provides a compound of formula (I) or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof for use in the treatment of hypertension, cardiovascular disease and certain eating disorders.

A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the general formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate, sodium lauryl sulphate or sucrose.

Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a hyperglycaemic human or non-human mammal in need thereof.

The present invention further provides a method for the treatment of hyperlipidaemia in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a hyperlipidaemic human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of hyperglycaemic humans, and/or the treatment and/or prophylaxis of hyperlipidaemic human, the compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be taken in doses, such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and more usually about 1 to 1500 mg.

In the treatment and/or prophylaxis of hyperglycaemic non-human mammals, especially dogs, the active ingredient may be adminstered by mouth, usually once

or twice a day and in an amount in the range of from about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg. Similar dosage regimens are suitable for the treatment and/or prophylaxis of hyperlipidaemia in non-human mammals.

The dosages regimens for the treatment of hypertension, cardiovascular disease and eating disorders will generally be those mentioned above in relation to hyperglycaemia.

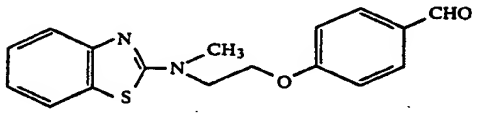
In a further aspect the present invention provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia.

The present invention also provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidaemia, hypertension, cardiovascular disease or certain eating disorders.

The following Procedures and Examples illustrate the invention but do not limit it in any way.

PREPARATION 1

4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]-benzaldehyde

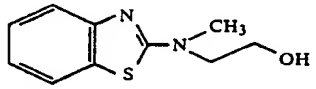


A mixture of 4-fluorobenzaldehyde (1.5g) and 2[N-methyl-N-(2-benzothiazolyl)amino]ethanol (2.4g) in sulphoxide (50 ml) containing anhydrous potassium carbonate (2 g) was stirred at 100° C. for 24 hours. The mixture was cooled to room temperature and added to water (300 ml). The aqueous solution was extracted with diethyl ether (2×300 ml). The organic extracts were washed with brine (1×300 ml), dried ($MgSO_4$), filtered and evaporated to dryness. The title compound was obtained as a waxy solid following chromatography on silica-gel in 1% methanol in dichloromethane.

^1H NMR δ ($CDCl_3$) 3.2 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 6.8–7.8 (8H, complex); 9.8 (1H, s).

PREPARATION 2

2-[N-Methyl-N-(2-benzothiazolyl)amino]ethanol

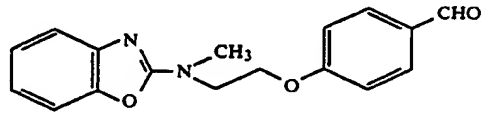


A mixture of 2-chlorobenzothiazole (8.5 g) and 2-methylaminoethanol (20 ml) was heated at 120° C. under pressure in a sealed, glass lined, stainless steel reaction vessel for 18 hours. After cooling, the oil was added to water (100 ml), extracted with dichloromethane (2×100 ml), the organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness Chromatography of the residual oil on silica-gel in 2½% methanol in dichloromethane gave the title compound which was used in Preparation 1 without further purification.

^1H NMR δ ($CDCl_3$) 3.15 (3H, s); 3.4–4.0 (4H, m); 4.7 (1H, broad s, exchanges with D_2O; 6.8–7.6 (4H, complex).

PREPARATION 3

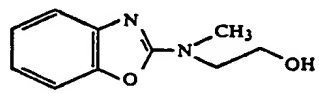
4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde



To a solutiOn of 2-[N-methyl-N-(2-benzoxazolyl) amino]ethanol (9.6 g), triphenylphosphine (13.1 g) and 4-hydroxybenzaldehyde (6.1 g) in dry tetrahydrofuran (150 ml) was added dropwise a solution of diethyl azodicarboxylate (9.0 g) in dry tetrahydrofuran (30 ml), under a blanket of nitrogen with stirring at room temperature. The solution was stirred overnight at room temperature following which the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether (300 ml), filtered and the ether solution was washed with dilute sodium hydroxide solution (200 ml), saturated brine (200 ml), dried ($MgSO_4$), filtered and the solvent evaporated. The title compound (mp 97°–98° C.) was obtained after chromatography on silica-gel, eluting with dichloromethane. ^1H NMR δ ($CDCl_3$) 3 30 (3H, s); 3.85 (2H, t); 4.30 (2H, t) 6.80–7.85 (8H, complex); 9.85 (1H, s).

PREPARATION 4

2-[N-Methyl-N-(2-benzoxazolyl)amino]ethanol

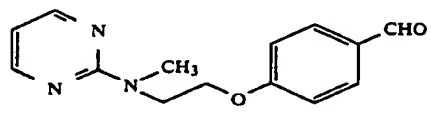


A solution of 2-chlorobenzoxazole (15.4 g) in dry tetrahydrofuran (50 ml) was added dropwise to an ice cooled solution of 2-methylaminoethanol (15.0 g) in dry tetrahydrofuran (100 ml) with stirring and protection from atmospheric moisture. The mixture was stirred at 0° C. for 1 hour, allowed to warm to room temperature and stirred for a further 2 hours. The solvent was removed under reduced pressure, the product was dissolved in ethyl acetate (200 ml) and washed with brine (2×150 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated. Chromatography of the residue on silica-gel in dichloromethane gave the title compound (mp 62°–3° C.) which was used in Preparation 3 without further purification.

^1H NMR δ ($CDCl_3$) 3.12 (3H s); 3.4–4.0 (4H, m); 4.7 (1H, s, exchanges with D_2O); 6.8–7.4 (4H, complex).

PREPARATION 5

4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy]benzaldehvde

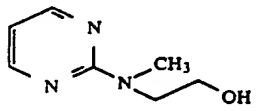


A mixture of 4-fluorobenzaldehyde (12 ml) and 2-[N-methyl-N-(2-pyrimidinyl)amino]ethanol (10.05 g) in dry dimethyl sulphoxide (50 ml) containing anhydrous potassium carbonate (15 g) was stirred at 120° C. for 6 hours. The mixture was cooled to room temperature and added to water (200 ml). The aqueous solution was extracted with ethyl acetate (2×300 ml), the organic extracts washed with brine, dried ($MgSO_4$) and evaporated. The title compound was obtained as an oil following chromatography on silica-gel in 2% methanol in dichloromethane.

^1H NMR δ ($CDCl_3$) 3.3 (3H, s); 3.8–4.4 (4H, complex); 6.5 (1H, t); 7.0 (2H, d); 7.8 (2H, d); 8.3 (2H, d); 9.9 (1H, s).

PREPARATION 6

2-[N-Methyl-N-(2-pvrimidinyl)amino]ethanol

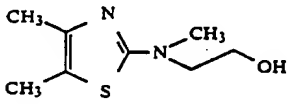


A mixture of 2-chloropyrimidine (10 g) and 2-methylaminoethanol in dry tetrahydrofuran (100 ml) was boiled under reflux for 3 hours. The solution was cooled, water (200 ml) was added, the mixture extracted with dichloromethane, the organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The residual oil was used in Preparation 5 without further purification.

^1H NMR δ ($CDCl_3$) 3.2 (3H, s); 3.5–3.9 (4H, m); 4.6 (1H, s, exchanges with D_2O); 6.4 (1H, t); 8.2 (2H, d).

PREPARATION 7

2-N-Methyl-N-(2-[4,5-dimethylthiazolyl])amino]ethanol

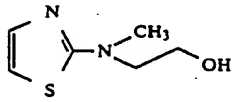


A solution of 2-chloro-4,5-dimethylthiazole (13.2 g) and 2-methylaminoethanol (40 ml) in pyridine (100 ml) was boiled under reflux for 20 hours. After cooling, the oil was added to water (300 ml) and extracted with ethyl acetate (3×200 ml). The organic extracts were washed with brine (2×200 ml), dried ($MgSO_4$), filtered and evaporated to dryness to leave the title compound which was used in Preparation 14 without further purification.

^1H NMR δ ($CDCl_3$) 2.15 (3H, s); 2.20 (3H, s); 3.1 (3H, s); 3.4–3.9 (4H, m); 5.25 (1H, broad s, exchanges with D_2O).

PREPARATION 8

2-[N-Methyl-N-(2-thiazolyl)amino]ethanol

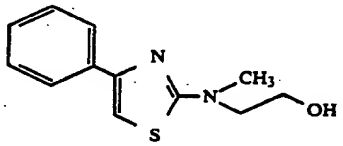


The title compound was prepared as an oil from 2-bromothiazole (15 g) and 2-0methylaminoethanol (45 ml) by an analogous procedure to that described in Preparation 7

^1H NMR δ ($CDCl_3$) 3.1 (3H, 2); 3.4–3.0 (4H, m); 4.8 (1H, broad s, exchanges with D_2O); 6.4 (1H, d); 7.0 (1H, d).

PREPARATION 9

2-[N-Methyl-N-(2-(4-phenylthiazolyl))amino]ethanol

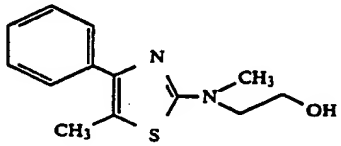


The title compound was prepared as an oil from 2-chloro-4-phenylthiazole (13.5 g) and 2-methylaminoethanol (40 ml) by an analogous procedure to that described in Preparation 7.

1H NMR δ ($CDCl_3$) 3.15 (3H, s); 3.6–4.0 (4H, m); 4.6 (1H, broad s, exchanges with D_2O); 6.7 (1H, s); 7.2–7.9 (5H, complex).

PREPARATION 10

2-[N-Methyl-N-(2-(4-phenyl-5-methylthiazolyl)-)amino]ethanol

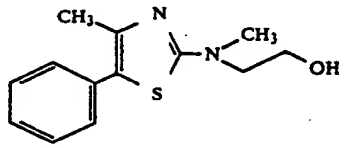


The title compound was prepared as an oil from 2-chloro-4-phenyl-5-methylthiazole (18.9 g) and 2-methylaminoethanol (50 ml) by an analogous procedure to that described in Preparation 7.

^1H NMR δ ($CDCl_3$) 2.38 (3H, s); 3.0 (3H, s); 3.45–3.85 (4H, m); 5.1 (1H, broad s, exchanges with D_2O); 7.1–7.7 (5H, complex).

PREPARATION 11

2-[N-Methyl-N-(2-(4-methyl-5-phenylthiazolyl)-)amino]ethanol

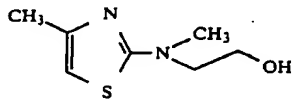


The title compound was prepared as an oil from 2-chloro-4-methyl-5-phenylthiazole (14.8 g) and 2-methylaminoethanol (40 ml) by an analogous procedure to that described in Preparation 7.

^1H NMR δ ($CDCl_3$) 2.35 (3H, s); 3.1 (3H, s); 3.5–4.0 (4H, m); 5.1 (1H, broad s, exchanges with D_2O); 7.1–7.5 (5H, complex).

PREPARATION 12

2-[N-Methyl-N-(2-(4-methylthiazolyl))amino]ethanol

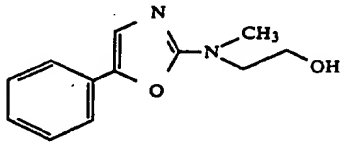


The tital compound was prepared, by an analogous procedure to that described in Preparation 7, and was used in the next stage without further purification.

^{1}H NMR δ ($CDCl_3$) 2.25 (3H, s); 3.1 (3H, s); 3.55–3.95 (4H, m); 4.9 (1H, broad s, exchanges with D_2O); 6.1 (1H, s).

PREPARATION 13

2-[N-Methyl-N-[2- (5-phenyloxazolyl)]amino]ethanol

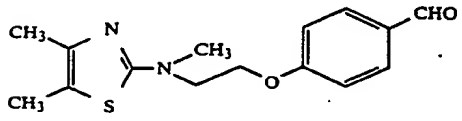


A solution of 2-chloro-5-phenyloxazole (8.3 g) and 2-methylaminoethanol (30 ml) was stirred at 50° C. for 10 minutes. After cooling the oil was added to water (250 ml) and extracted with ethyl acetate (2×150 ml). The organic extracts were washed with brine (2×100 ml), dried ($MgSO_4$), filtered and evaporated to dryness to leave the title compound (m.p. 73°–75° C.).

^{1}H NMR δ ($CDCl_3$) 3.2 (3H, s); 3.6 (2H, t); 3.85 (2H, t); 3.9 (1H, broad s, exchanges with D2O); 7.0 (1H, s); 7 2–7.55 (5H, complex).

PREPARATION 14

4-[2-(N-Methyl-N-(2-(4,5-dimethylthiazolyl)amino) ethoxy)]benzaldehyde

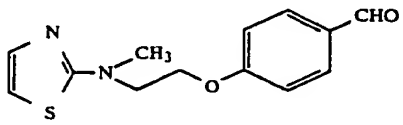


The title compound was prepared from 2-[N-methyl-N(2-(4,5-dimethylthiazolyl))amino]ethanol (13.2 g) and 4-fluorobenzaldehyde (23.1 g) by an analogous procedure to that described in Preparation 5.

^{1}H NMR δ ($CDCl_3$) 2.15 (3H, s); 2.2 (3H, s); 3.18 (3H, s); 3.8 (2H, t); 4.3 (2H, t); 7.0 (2H, d); 7.8 (2H, d); 10.0 (1H, s).

PREPARATION 15

4-[2-(N-Methyl-N-(2-thiazolyl)amino)ethoxy]benzaldehyde

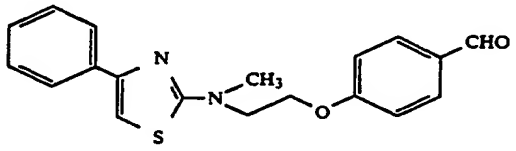


The title compound was prepared from 2-[N-methyl-N-(2-thiazolyl)amino]ethanol (10.7 g) and 4-fluorobenzaldehyde (15.9 g) by an analogous procedure to that described in Preparation 5.

^{1}H NMR δ ($CDCl_3$) 3.15 (3H, s); 3.9 (2H, t); 4.4 (2H, t); 6.5 (1H, d); 7.0 (2H, d); 7.15 (1H, d); 7.8 (2H, d); 9.9 (1H, s).

PREPARATION 16

4-[2-(N-Methyl-N-(2-(4-phenylthiazolyl)amino)ethoxy)]benzaldehyde

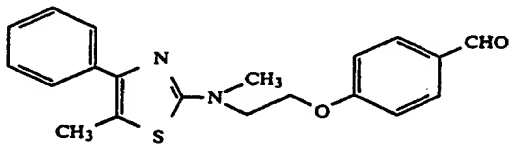


The title compound was prepared from 2-[N-methyl-N-(2-(4-phenylthiazolyl))amino]ethanol (16.1 g) and 4-fluorobenzaldehyde (17.4 g) by an analogous procedure to that described in Preparation 5.

^{1}H NMR δ ($CDCl_3$) 3.2 (3H, s); 3.95 (2H, t); 4.3 (2H, t); 6.7 (1H, s); 6.95–7.9 (9H, complex); 9.9 (1H, s).

PREPARATION 17

2-(N-Methyl-N-(2-(4-phenyl-5-methylthiazolyl)amino) ethoxy)1benzaldehyde

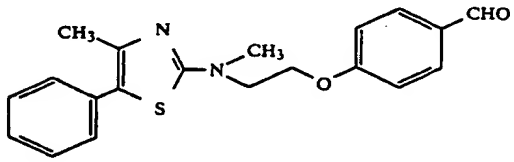


The title compound was prepared from 2-[N-methyl-N-(2-(4-phenyl-5-methylthiazolyl))amino]ethanol (13 g) and 4-fluorobenzaldehyde (9.8 g) by a similar procedure to that described in Preparation 5.

^{1}H NMR δ ($CDCl_3$) 2.35 (3H, s); 3.1 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 6.85–7.8 (9H, complex); 9.85 (1H, s).

PREPARATION 18

4-[2-(N-Methyl-N-(2-(4-methyl-5-phenyl-thiazolyl-)amino) ethoxy)]benzaldehyde

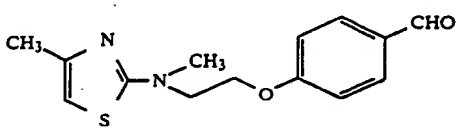


The title compound was prepared from 2-[N-methyl-N-(2-(4methyl-5-phenylthiazolyl))amino]ethanol (13 g) and 4-fluorobenzaldehyde (13 g) by an analogous procedure to that described in Preparation 5.

^{1}H NMR δ ($CDCl_3$) 2.36 (3H, s); 3.2 (3H, s); 3.9 (2H, t); 4.35 (2H, t); 7.05 (2H, d); 7.2–7.5 (5H, complex); 7.85 (2H, d); 9.95 (1H, s).

PREPARATION 19

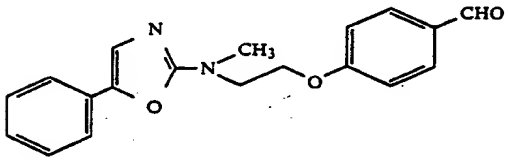
4-[2-(N-Methyl-N-(2-(4-methylthiazolyl))amino)ethoxy]benzaldehyde



The title compound was prepared from 2-[N-methyl-N-(2-(4-methylthiazolyl))amino]ethanol (12 g) and 4-fluorobenzaldehyde (14.3 g) by an analogous procedure to that described in Preparation 5. ^{1}H NMR 4 ($CDCl_3$) 2.25 (3H, s); 3.2 (3H, s); 3.9(2H, t); 4.3 (2H, t); 6.1 (1H, s); 7.05 (2H, d); 7.85 (2H, d); 9.95 (1H, s).

PREPARATION 20

4-[2-(N-Methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy]benzaldehyde

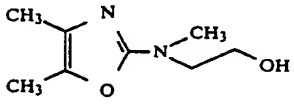


The title compound was prepared from 2-[N-methyl-N-(2-(5-phenyloxazolyl))amino]ethanol (9.3 g) and 4-fluorobenzaldehyde (7.9 g) by an analogous procedure to that described in Preparation 5.

^{1}H NMR δ ($CDCl_3$) 3.25 (3H, s); 3.85 (2H, t); 4.3 (2H, t); 6.95–7.6 (8H, complex); 7.8 (2H, d); 9.9 (1H, s).

PREPARATION 21

2-[N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino]-ethanol.

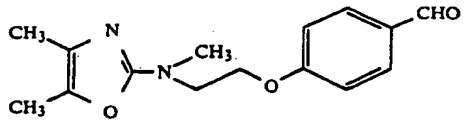


A solution of 2-chloro-4,5-dimethyloxazole (5 g) and 2-methylaminoethanol (15 ml) was stirred at 120° C. for 40 minutes. After cooling the oil was added to water (200 ml) and extracted with dichloromethane (3×200 ml). The organic extracts were washed with brine (2×100 ml), dried ($MgSO_4$), filtered and evaporated to dryness to leave the title compound as a waxy solid, which was used in Preparation 22 without further purification.

^{1}H NMR δ ($CDCl_3$) 1.95 (3H, s); 2.10 (3H, s); 3.05 (3H, s); 3.5 (2H, t); 3.8 (2H, t); 4.4 (1H, broad s, exchanges with D_2O).

PREPARATION 22

4-[2-(N-Methyl-N-2-(4,5-dimethyloxazolyl)]amino) ethoxy]benzaldehyde

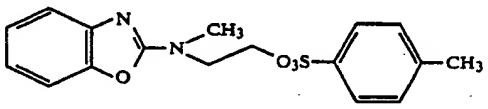


To a stirred solution of 2-[N-methyl-N-[2-(4,5dimethyloxazolyl)amino]ethanol (2.7 g) in DMF (60 ml), under an atmosphere of nitrogen, was added portionwise sodium hydride (0.7 g; 60% dispersion in oil). After the vigorous reaction had subsided, 4-fluorobenzaldehyde (2.9 g) was added and the reaction mixture was heated to 80° C. for 16 hours. After cooling, the mixture was added to water (400 ml). The aqueous solution was extracted with diethyl ether (3×250 ml). The organic extracts were washed with brine (2×100 ml), dried ($MgSO_4$), filtered and evaporated to dryness. The title compound was obtained as an oil following chromatography of the residue on silica-gel in 1% methanol in dichloromethane.

^{1}H NMR δ ($CDCl_3$) 1.95 (3H, s); 2.15 (3H, s); 3.15 (3H, s); 3.8 (2H, t); 4.25 (2H, t); 7.0 (2H, d); 7.9 (2H, d); 10.0 (1H, s).

PREPARATION 23

2-(N-(2-Benzoxazolyl)-N-methylamino)ethanol 4-toluenesulphonyl ester

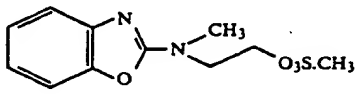


4-Toluenesulphonyl chloride (19.0 g) was added portionwise to a solution of N-(2-benzoxazolyl)-N-methylaminoethanol (19.2 g) in dry pyridine (100 ml) at room temperature. The mixture was stirred at room temperature for 3 hours, added to water (500 ml) and extracted with dichloromethane (3×250 ml). The combined extracts were washed with 2M hydrochloric acid (3×250 ml), saturated sodium bicarbonate solution (250 ml) and brine (250 ml), dried ($MgSO_4$), filtered and evaporated. The title compound was obtained pure following crystallisation from ethanol (m.p. 119°–121° C.).

^{1}H NMR δ (DMSO-d_6) 2.25 (3H, s); 3.05 (3H, s); 3.75 (2H, t); 4.35 (2H, t); 7.0–7.4 (6H, complex); 7.70 (2H, d).

PREPARATION 24

2-(N-(2-Benzoxazolyl)-N-methylamino)ethanol methanesulphonyl ester

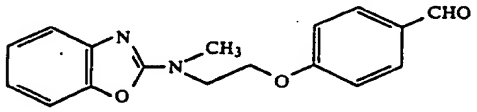


The title compound (m.p. 97°–8° C.) was prepared from N-(2-benzoxazolyl)-N-methylaminoethanol (19.2 g) and methanesulphonyl chloride (11.5 g) by a similar procedure to that used in Preparation 23.

^{1}H NMR δ ($CDCl_3$) 2.90 (3H, s); 3.25 (3H, s); 3.7 (2H, t); 4.5 (2H, t); 6.90–7.4 (4H, complex).

PREPARATION 25

4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde

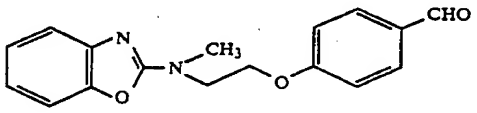


To a solution of 4-hydroxybenzaldehyde (7.32 g) in dry dimethylformamide (100 ml) was added portionwise sodium hydride (60%, 2.4 g) with stirring at room temperature under nitrogen. When gas evolution ceased a solution of 2-(N-methyl-N-(2-benzoxazolyl)amino)ethanol 4-toluenesulphonyl ester (17.3 g) in dry dimethylformamide was added dropwise The mixture was heated to 80° C. and stirred at this temperature overnight. After cooling, the solution was poured into iced water (1 litre), extracted with ethyl acetate (3×500 ml); and the combined extracts were washed with sodium hydroxide solution (2M; 500 ml) and brine (500 ml), dried ($MgSO_4$), filtered and evaporated. The title compound (m.p. 96°–98° C.) was obtained pure after crystallisation from ethanol.

^{1}H NMR δ (DMSO-d_6) 3.25 (3H, s); 3.95 (2H, t); 4.40 (2H, t); 6.90–7.40 (6H, complex); 7.85 (2H, d); 9.90 (1H, s).

PREPARATION 26

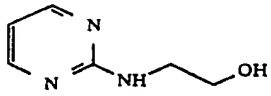
4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde



The title compound was prepared from 4-hydroxy benzaldehyde (1.22 g) and 2-(N-methyl-N-(2-benzoxazolyl)-amino)ethanol methanesulphonyl ester (2.7 g) in a similar manner to that described in Preparation 25.

PREPARATION 27

2-(2-Pyrimidinylamino)ethanol

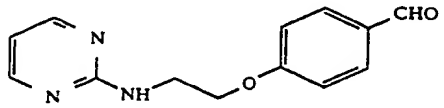


2-Chloropyrimidine (5 g) and ethanolamine (15 ml) were stirred for 2 hours at 140° C. After cooling, the mixture was added to water (200 ml) and continuously extracted with ethyl acetate (500 ml) for 16 hours. The organic extract was dried ($MgSO_4$), filtered and evaporated to dryness. The title compound was obtained as a solid (m.p. 66° C.), following chromatography on silica-gel in 3% methanol in dichloromethane.

^{1}H NMR δ ($CDCl_3$) 3.55 (2H, complex); 3.8 (2H, t); 4.3 (1H, broad s, exchanges with D_2O); 6.1 (1H, broad s, exchanges with D_2O); 6.55 (1H, t); 8.3 (2H, d).

PREPARATION 28

4-[2-(2-Pyrimidinylamino)ethoxy]benzaldehyde

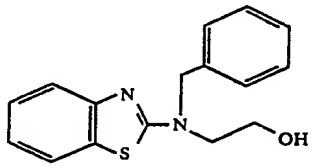


Sodium hydride (1.2 g; 60% dispersion in oil) was added portionwise to a stirred solution of 2-(2-pyrimidinyl amino)ethanol (4 g) in DMF (140 ml) under an atmosphere of nitrogen. After the vigorous reaction had subsided 4-fluorobenzaldehyde (5.35 g) was added and the solution heated to 80° C. for 20 hours. After cooling the mixture was added to water (500 ml) and extracted with diethyl ether (3×300 ml). The organic extracts were washed with brine (2×200 ml), dried ($MgSO_4$), filtered and evaporated to dryness. Chromatography of the residue on silica gel in 2% methanol in dichloromethane afforded the title compound, which was used in the next stage without further purification.

^{1}H NMR δ ($CDCl_3$) 3.8 (2H, complex); 4.2 (2H, t); 5.7 (1H, broad s, exchanges with D_2O); 6.5 (1H, t); 7.0 (2H, d); 7.8 (2H, d); 8.3 (2H, d); 9.9 (1H, s).

PREPARATION 29

2-(N-(2-Benzothiazolyl)-N-benzylamino)ethanol

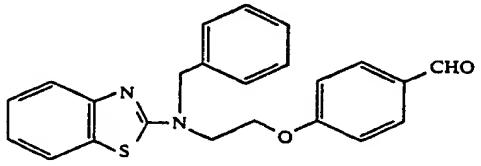


2-Chlorobenzothiazole (13 g) and 2-(benzylamino)ethanol (29 g) were heated together in a sealed vessel at 120° C. for 20 h. After cooling, the reaction mixture was dissolved in ethyl acetate (200 ml) and the solution was washed with saturated aqueous sodium hydrogen carbonate (3×100 ml), water (3×100 ml) and brine (100 ml), dried over anhydrous magnesium sulphate and evaporated to give the title compound (m.p. 95°–96° C.; dichloromethane/hexane).

^{1}H NMR δ ($CDCl_3$) 3.8 (4H, m); 4.5 (1H, broad s, exchanges with D_2O); 4.7 (2H, s); 6.9–7.7 (9H, complex).

PREPARATION 30

4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy)benzaldehyde



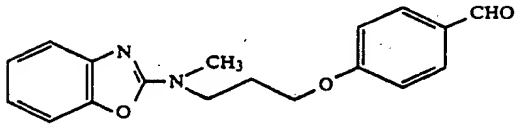
The title compound was prepared from 2-(N-(2-benzothiazolyl)-N-benzylamino)ethanol (8.25 g) and 4-

fluorobenzaldehyde (3.6 g) by an analogous procedure to that described in Preparation 22.

^{1}H NMR δ ($CDCl_3$) 4.0 (2h, t); 4.4 (2H, t); 4.9 (2H, s); 6.9–8.0 (13H, complex); 10.0 (1H, s).

PREPARATION 31

4-3-(N-Methyl-N-(2-benzoxazolyl)-amino)propoxy]-benzaldehyde

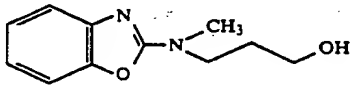


The title compound was prepared from 3-[(N-(2-benzoxazolyl)-N-methyl)amino]propan-1-ol (7.5 g) and 4-fluorobenzaldehyde (6.78 g) by a similar procedure to that described in Preparation 22.

^{1}H NMR δ ($CDCl_3$) 2.0–2.4 (2H, complex); 3.2 (3H, s); 3.75 (2H, t); 4.2 (2H, t); 6.8–7.5 (6H, complex); 7.8 (2H, d); 9.9 (1H, s).

PREPARATION 32

3-[(N-(2-Benzoxazolyl)-N-methyl)amino]propan-1-ol

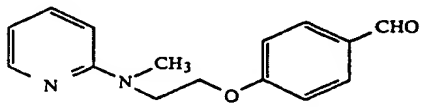


2-Chlorobenzoxazole (15.36 g) in dry tetrahydrofuran (50 ml) was added dropwise to a mixture of 3-N-methylaminopropan-1-ol (9.8 g) and triethylamine (20.2 g) in dry tetrahydrofuran (130 ml) with stirring, at room temperature. After stirring at room temperature overnight the solvent was evaporated. The residue was dissolved in dichloromethane (150 ml), washed with water (3×100 ml), brine (150 ml), dried ($MgSO_4$), filtered and evaporated. The title compound was obtained as an oil following chromatography on silica-gel in 2.5–3% methanol in dichloromethane.

^{1}H NMR δ ($CDCl_3$) 1.8–2 1 (2H, complex); 3.2 (3H, s); 3.5–3.85 (4H, complex); 4.3 (1H, broad s, exchanges with D_2O); 6.8–7.5 (4H, complex).

PREPARATION 33

4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzaldehyde

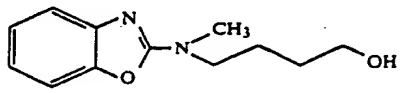


The title compound was prepared from 2-(N-methyl-N-(2-pyridyl)amino)ethanol (8.9 g) and 4-fluorobenzaldehyde by a similar procedure to that described in Preparation 22.

^{1}H NMR δ ($CDCl_3$) 3.2 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 6.4 (2H, t); 6.9 (2H, d); 7.3 (1H, complex); 7.75 (2H,d); 8.15 (1H,d); 9.9 (1H, s).

PREPARATION 34

4-[N-(2-Benzoxazoyl)-N-methylamino1butan-1-ol

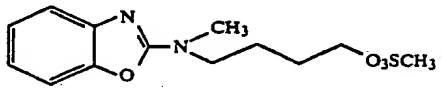


2-Chlorobenzoxazole (15.35 g) was added dropwise over 10 minutes to a stirred solution of 4-(N-m ®thylamino)butan-1-ol (10.3 g) and triethylamine (20.3 g) in dry tetrahydrofuran (150 ml). The mixture was stirred at room temperature overnight, and then heated at reflux for a further 2 h. The resulting mixture was cooled and the solvent was evaporated. The residue was dissolved in dichloromethane (500 ml), washed with saturated sodium bicarbonate solution (3×300 ml) and brine (500 ml), dried and evaporated to afford the title compound as an oil.

^{1}H NMR δ ($CDCl_3$) 1.5–2.0 (4H, complex); 3.1 (3H,s); 3.4–3.9 (5H, complex; reduced to 4H after D20 exchange); 6.9–7.4 (4H, complex)

PREPARATION 35

4-[(N-(2-BenzoxazolVl)-N-methyl)amino1butan-l-ol methanesulohonyl ester

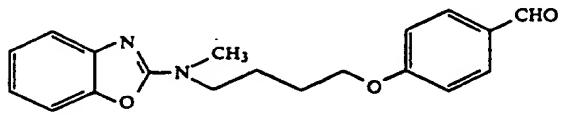


Methanesulphonyl chloride (3.15 g) was added dropwise to a stirred, ice-cooled solution of 4-[N-(2-benzoxazolyl)-N-methylamino]butan-1-ol (5.5 g) and 4-dimethylaminopyridine (0.15 g) in pyridine (100 ml). The mixture was allowed to warm to room temperature overnight, and then diluted with water (500 ml), and extracted with dichloromethane (3×200 ml). The combined extracts were washed with saturated sodium bicarbonate solution (3×200 ml), and brine (200 ml), then dried and the solvent evaporated to afford an oil. More of this oil was obtained from the acidic aqueous layers by means of adjusting the pH to 4.5 with solid potassium carbonate, re-extracting with dichloromethane (3×200 ml), and drying and evaporating these dichloromethane layers. The combined impure product fractions were chromatographed on silica gel with 2% methanol in dichloromethane as eluent to afford the title compound as an oil.

^{1}H NMR δ ($CDCl_3$) 1.80(4H,complex); 3.05(3H,s); 3.25(3H,s); 3.60(2H,complex); 4.30(2H,complex); 6.90–7.40(4H, complex)

PREPARATION 36

4-[4-(N-Methyl-N-(2-benzoxazolyl)amino)butoxy]benzaldehyde

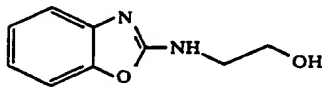


The title compound was prepared from 4-hydroxybenzaldehyde (1.71 g) and 4-[N-(2-benzoxazolyl)-N-methylamino]butan-1-ol methanesulphonyl ester (3.80 g) by a similar procedure to that used in Preparation 26.

^{1}H NMR δ ($CDCl_3$) 1.70–1.95(4H, complex); 3.20(3H,s); 3.55(2H, complex); 4.00(2H, complex); 6.80–7.40(6H, complex) 7.75(2H,d); 9.90(1H,s)

PREPARATION 37

2-[N-(2-Benzoxazolyl)amino]ethanol

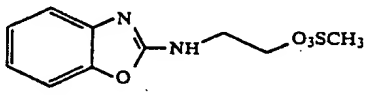


A solution of 2-chlorobenzoxazole (12.78 g) in dry tetrahydrofuran (50 ml) was added, over 10 minutes, to a stirred, ice-cooled solution of ethanolamine (15.3 g) in dry tetrahydrofuran (400 ml). The mixture was heated at reflux overnight, cooled, and the solvent evaporated. The residue was partitioned between water (500 ml) and dichloromethane (500 ml), and the resulting white solid filtered off, washed with dichloromethane and dried in vacuo to afford the title compound m.p. 162°–4° C.

^{1}H NMR δ DMSO-d_6 3.3–3.8 (4H, complex); 5.0 (1H, br, exchanges with D_2O); 6.9–7.7 (4H, complex); 8.1 (1H, br, exchanges with D_2O).

PREPARATION 38

2-[N-(2-Benzoxazolyl)aminolethanol methanesulphonyl ester



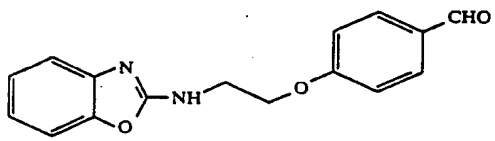
Methanesulphonyl chloride (4.9 g) was added dropwise to a stirred, ice-cooled solution of 2-[N-(2-benzoxazolyl-)amino]ethanol (6.23 g) and triethylamine (4.39 g) in dichloromethane (75 ml). The resulting mixture was stirred at 0° C. for 1.5h and then diluted with dichloromethane (200 ml), washed with water (2×200 ml), brine (200 ml) and dried. The dichloromethane layer was evaporated and the residue chromatographed on silica gel with 1.5% methanol in dichloromethane as eluent to give the title compound,

m.p. 96°–9° C..

^{1}H NMR δ $CDCl_3$ 3.0 (3H,s); 3.85 (2H,t); 4.5 (2H,t); 5.9 (1H,br, exchanges with D_2O); 7.0–7.5 (4H, complex).

PREPARATION 39

4-[2-(N-(2-Benzoxazolyl)amino)ethoxy]benzaldehyde

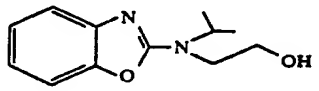


A mechanically stirred r'ixture of 2-[N-(2-benzoxazolyl-)amino]ethanol methanesulphonyl ester (5.77 g), 4-hydroxybenzaldehyde (2.81 g) and potassium carbonate (3.28 g) was heated at 80° C. overnight in dry DMF (250 ml). After cooling, the reaction mixture was concentrated in vacuo, diluted with water (500 ml) and extracted with ethyl acetate (3×300 ml). The combined ethyl acetate layers were washed with water (2×11). brine (11), dried and evaporated. The resulting solid was chromatographed on silica gel with 1.5% methanol in dichloromethane as eluent to afford the title compound, m.p. 103°–6° C.

^{1}H NMR δ $CDCl_3$ 3.9 (2H,t); 4.3 (2H,t); 6.4 (1H, br, exchanges with D_2O); 6.9–8.0 (8H, complex); 9.9 (1H,s).

PREPARATION 40

2-[N-Isopropyl-N-(2-benzoxazolyl)amino]ethanol

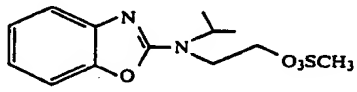


2-Chlorobenzoxazole (23.04 g) was added dropwise to an ice-cooled solution of 2-(isopropylamino)ethanol (15.45 g) and triethylamine (30.3 g) in tetrahydrofuran (500 ml). The mixture was stirred at room temperature for 30 minutes, then heated at reflux overnight before being cooled and evaporated. The residue was dissolved in dichloromethane (800 ml) and washed with saturated sodium bicarbonate solution (500 ml), water (3×11) brine (11), dried ($MgSO_4$), filtered and evaporated. The title compound was obtained as an oil following chromatography on silica gel using 1.5% methanol-dichloromethane as solvent.

^{1}H NMR δ ($CDCl_3$) 1.25 (6H,d); 3.6 (2H,t); 3.9 (2H,t); 4.5 (1H,m); 4.55 (1H, broad s, exchanges with D_2O); 6.95–7.50 (4H, complex).

PREPARATION 41

2-[N-Isopropyl-N-(2-benzoxazolyl)amino]ethanol methanesulchonyl ester.

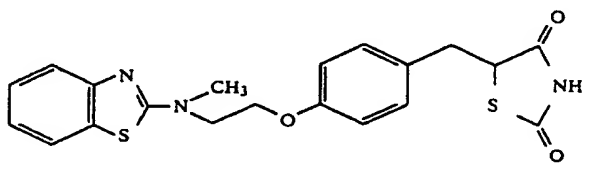


The title compound was prepared from 2-[N-isopropyl-N-(2-benzoxazolyl)amino]ethanol and methanesulphonyl chloride by a similar procedure to that described in Preparation 38.

^{1}H NMR δ ($CDCl_3$) 1.35 (6H,d); 3.0 (3H,s); 3.8 (2H,t); 4.3–4.7 (3H, complex); 6.9–7.5 (4H, complex).

EXAMPLE 1

5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]-benzyl)-2,4-thiazolidinedione.



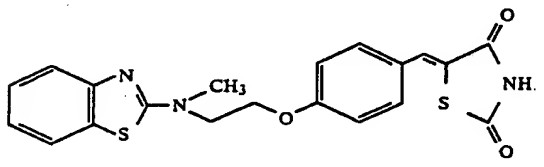
5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione (2g) in dry 1,4-dioxan (70 ml) was reduced under hydrogen in the

presence of 10% palladium on charcoal (3 g) at ambient temperature and atmospheric pressure until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates were evaporated to dryness under vacuum. The title compound (m.p. 167°–8° C.) was obtained after crystallisation from methanol.

^{1}H NMR δ (DMSO-d_6) 2.9–3.4 (2H, complex); 3.25 (3H, s); 3.9 (2H, complex); 4.25 (2H, complex); 4.8 (1H, complex); 6.8–7.75 (8H, complex); 12.0 (1H, s, exchanges with D20).

EXAMPLE 2

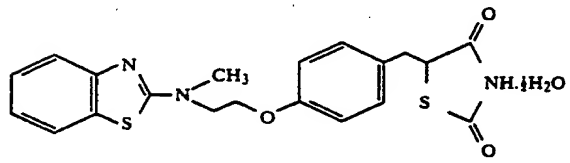
5-(4-[2-(N-Methyl-N-(2-benzothiazolyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione.



A solution of 4-[2-(N-methyl-N-(2-benzothiazolyl-)amino) ethoxy]benzaldehyde (1.9 g) and 2,4-thiazolidinedione (0.8 g) in toluene (100 ml) containing a catalytic quantity of piperidinium acetate was boiled under reflux in a Dean and Stark apparatus for 2 hours. The mixture was cooled and filtered and the filtered solid was dried to give the title compound (mp 219° C.). ^{1}H NMR δ (DMSO-d_6) 3.2 (3H, s); 3.9 (2H, t); 4.35 (2H, t); 6.8 –7.7 (10H, complex).

EXAMPLE 3

5-(4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxyl]-benzyl)-2,4-thiazolidinedione hemihydrate



5-(4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione (1.5 g) in dry 1,4-dioxan (80 ml) was reduced under hydrogen in the presence of 10% palladium on charcoal (2 g) at ambient temperature and atmospheric pressure until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates were evaporated to dryness under vacuum. The title compound (mp 147°–9° C.) was obtained after crystallisation from methanol.

^{1}H NMR δ (DMSO-d_6+D_2O)

3.1–3.5 (2H, complex); 3.3 (3H,s); 3.95 (2H, complex); 4.25 (2H, complex); 4.5 (1H, complex); 6.8–7.3 (8H, complex).

EXAMPLE 4

5-(4-[2-(N-Methyl-N-(2-benzoxazolyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione

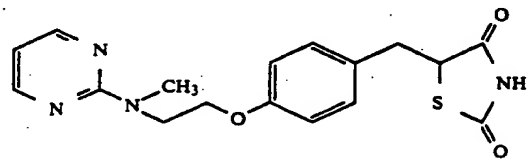
A solution of 4-[2-(N-methyl-N-(2-benzoxazolyl)amino) ethoxy]benzaldehyde (1.6 g) and 2,4-thiazolidinedione (0.63 g) in toluene (100 ml) containing a catalytic quantity of piperidinium acetate was boiled under reflux in a Dean and Stark apparatus for 2 hours. The mixture was cooled and filtered to give the title compound (mp 227°–9° C.).

^{1}H NMR δ (DMSO-d_6)

3.20 (3H, s); 3.90 (2H, t); 4.30 (2H, t); 6.9 –7.75 (10H, complex).

EXAMPLE 5

5-(4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione



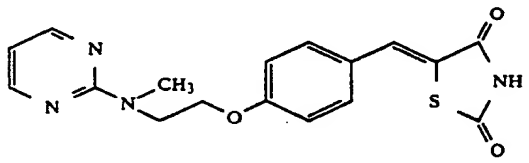
5-(4-[2-(N-Methyl-N-(2-pyrimidinyl)amino) ethoxy]-benzylidene)-2,4-thiazolidinedione (2.4 g) in dry 1,4-dioxan (150 ml) was reduced under hydrogen in the presence of 10% palladium on charcoal (3 g) until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates were evaporated to dryness under vacuum. The title compound (mp 150°–51° C.) was obtained after crystallisation from methanol.

^{1}H NMR δ (DMSO-d_6)

2.9–3.4 (2H, complex); 3.2 (3H, s); 3.9 (2H, complex); 4.2 (2H, complex); 4.9 (1H, complex); 6.6 (1H, t); 6.9 (2H, d); 7.2 (2H, d); 8.4 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 6

5-(4-[2-(N-Methyl-N-(2-pyrimidinyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione

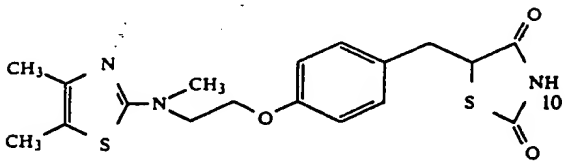


A solution of 4-[2-(N-methyl-N-(2-pyrimidinyl)amino) ethoxy]benzaldehyde (1.7 g) and 2,4-thiazolidinedione (0.7 g) in toluene (100 ml) containing a catalytic quantity of piperidinium acetate was boiled under reflux in a Dean and Stark apparatus for 2 hours. The mixture was cooled and filtered to give the title compound (mp 189°–90° C.).

^{1}H NMR δ (DMSO-d_6+D_2O) 3.2 (3H, s); 3.7–4.4 (4H, complex); 6.6 (1H, t); 7.1 (2H, d), 7.5 (2H, d); 7.7 (1H, s); 8.4 (2H, d).

EXAMPLE 7

5-(4-(2-(N-Methyl-N-[2-(4,5-dimethylthiazolyl)]amino) ethoxy]benzyl)-2,4-thiazolidinedione

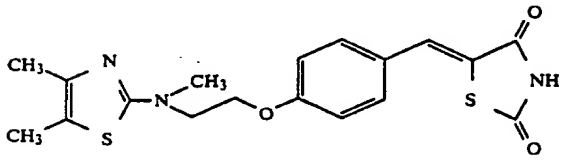


5-(4-[2-(N-Methyl-N-[2-(4,5-dimethylthiazolyl)]amino) ethoxy]benzylidene-2,4-thiazolidinedione (1.6 g) was dissolved in a mixture of methanol (50 ml) and dioxan (50 ml). Magnesium turnings (1.5 g) were added and the solution stirred until no more effervescence was observed. The mixture was added to water (300 ml), acidified (2M HCl) to form a solution, neutralised (saturated $NaHCO_3$ solution), filtered and dried. The solid was dissolved in dioxan (100 ml), adsorbed onto silica (20 g) and the title compound (m.p. 177° C.; MeOH) obtained following chromatography on silica-gel in 5% dioxan in dichloromethane.

^1H NMR δ (DMSO-d_6) 2.05 (3H, s); 2.15 (3H, s); 3.0 (3H, s); 3.0–3.4 (2H, complex); 3.8 (2H, t); 4.2 (2H, t); 4.85 (1H, complex); 6.9 (2H, d); 7.1 (2H, d); 12.0 (1H, broad s exchanges with D_2O).

EXAMPLE 8

2-(N-Methyl-N-2-(4,5-dimethylthiazolyl)]amino) ethoxy1benzylidene)-2,4-thiazolidinedione

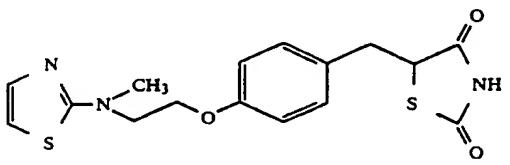


The title compound (m.p. 175° C.) was prepared by a similar procedure to that described in Example 4.

^1H NMR δ (DMSO-d_6) 2.0 (3H, s); 2.1 (3H, s); 3.0 (3H, s); 3.7 (2H, t); 4.25 (2H, t); 7.1 (2H, d); 7.55 (2H, d); 7.75 (1H, s); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 9

5-(4–2-(N-Methyl-N-(2-thiazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione

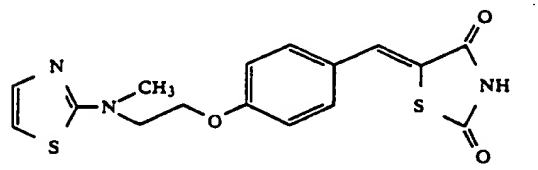


The title compound (m.p. 186° C.; MeOH) was prepared by an analogous procedure to that described in Example 7.

^1H NMR δ (DMSO-d_6) 3.0–3.4 (2H, complex); 3.1 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 4.85 (1H, complex); 6.7–7.3 (6H, complex); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 10

5-(4-[2-(N-Methyl-N-(2-thiazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione

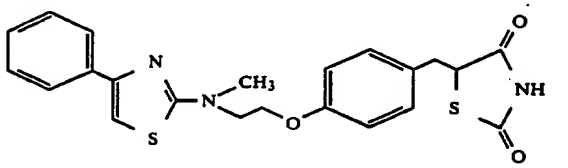


The title compound (m.p. 212° C.) was prepared by a similar procedure to that described in Example 4.

^1H NMR δ (DMSO-d_6) 3.1 (3H, s); 3.85 (2H, t); 4.3(2H, t); 6.75 (1H, d); 7.1–7.3 (3H, complex); 7.6 (2H, d); 7.75 (1H, s); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 11

5-[4-(2-(N-Methyl-N-(2-(4-phenylthiazolyl))amino) ethoxy)benzyl]-2,4-thiazolidinedione

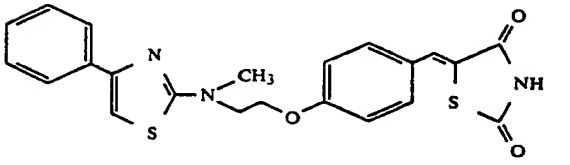


The title compound was obtained as a foam (m.p. 62°–65° C.) from 5-[4-(2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy)benzylidene]-2,4-thiazolidinedione (1.6 g) by a similar procedure to that described in Example 7.

^1H NMR δ (DMSO-d_6) 3.15 (3H, s); 3.0–3.4 (2H, complex); 3.9 (2H, t); 4.25 (2H, t); 4.85 (1H complex); 6.9 (2H, d); 7.1–7.45 (6H, complex); 7.85 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 12

5-(4–2-(N-Methyl-N-(2-(4-phenylthiazolyl))amino) ethoxy1benzylidene)-2,4-thiazolidinedione

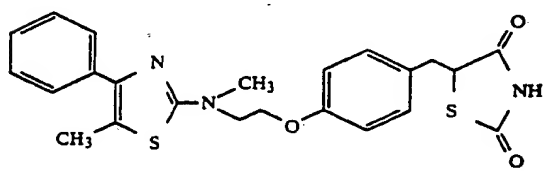


The title compound (m.p. 134° C.) was prepared from 4-[2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy]benzaldehyde by a similar procedure to that described in Example 4.

^1H NMR δ (DMSO-d_6) 3.2 (3H, s); 3.9 (2H, t); 4.35 (2H, t); 7.1–7.95 (11H, complex); 12.0 (1H broad s, exchanges with D_2O).

EXAMPLE 13

5-(4–2-(N-Methyl-N-[2-(4-phenyl-5-methylthiazolyl)-]amino)ethoxy]benzyl)-2,4-thiazolidinedione



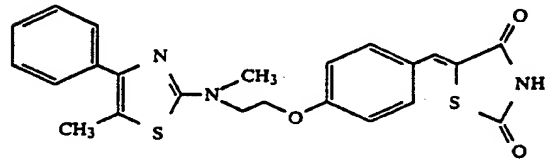
The title compound, obtained as a foam (m.p. 60°–62° C.), was prepared by an analogous procedure to that described in Example 7.

^{1}H NMR δ (DMSO-d_6) 2.35 (3H, s); 3.1 (3H, s); 3.0–3.4 (2H, complex); 3.8 (2H, t); 4.2 (2H, t); 4.85 (1H, complex);

6.9 (2H, d); 7.2 (2H, d); 7.25–7.5 (3H, complex); 7.65 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 14

5-(4[2-(N-Methyl-N-[2-(4-phenyl-5-methylthiazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione

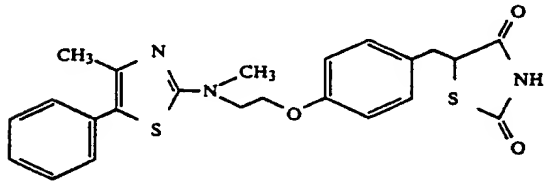


The title compound was prepared from 4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)]amino)ethoxy]benzaldehyde by a similar procedure to that described in Example 4, and was used in Example 13 without further purification.

^{1}H NMR δ (DMSO-d_6) 2.4 (3H, s); 3.1 (3H, s); 3.8 (2H, t); 4.35 (2H, t); 7.1–7.75 (10H, complex); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 15

5-(4-[2-(N-Methyl-N-[2-(4-methyl-5-phenylthiazolyl)-]amino)ethoxy]benzyl)-2,4-thiazolidinedione

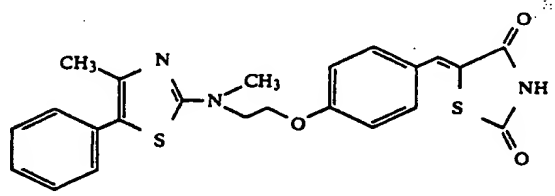


The title compound (m.p. 174° C.; MeOH) was prepared from 5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]amino)ethoxy]benzylidene)2,4-thiazolidinedione by an analogous procedure to that described in Example 7.

^{1}H NMR δ (DMSO-d_6) 2.3 (3H, s); 3.0–3.4 (2H, complex); 3.15 (3H, s); 3.85 (2H, t); 4.25 (2H, t); 4.85 (1H, complex); 6.95 (2H, d); 7.2 (2H, d); 7.45 (5H, complex); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 16

5-(4[2-(N-Methyl-N-2-(4-methyl-5-phenylthiazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione

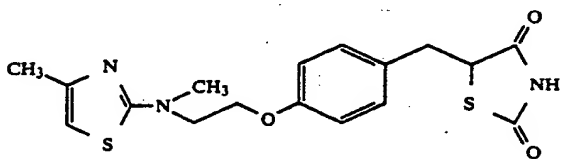


The title compound was prepared from 4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]amino)ethoxy]benzaldehyde by a similar procedure to that described in Example 4, and was used in Example 15 without further purification.

^{1}H NMR δ (DMSO-d_6) 2.3 (3H, s); 3.1 (3H, s); 3.85 (2H, t); 4.35 (2H, t); 7.15–7.75 (10H, complex); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 17

5-(4-[2-(N-Methyl-N-2-(4-methylthiazolyl)]amino)ethoxy]benzyl)-2,4-thiazolidinedione

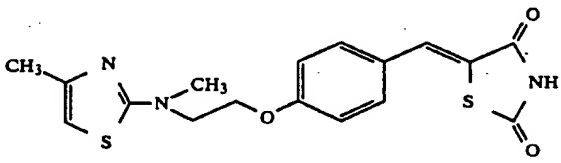


The title compound, was prepared from 5-(4-[2-(N-methyl -N-[2-(4-methylthiazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione as a foam (m.p. 121° C.), by a similar procedure to that described in Example 7.

^{1}H NMR δ (DMSO-d_6) 2.1 (3H, s); 3.0–3.4 (2H, complex); 3.1 (3H, s); 3.75 (2H, t); 4.15 (2H, t); 4.85 (1H, complex); 6.3 (1H, s); 6.9 (2H, d); 7.2 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 18

5-(4–2-(N-Methyl-N-[2-(4-methylthiazolyl)]amino) ethoxy]benzylidene)-2,4-thiazolidinedione

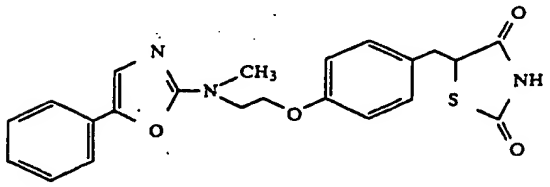


The title compound was prepared from 5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]amino)ethoxy]benzaldehyde by a similar procedure to that described in Example 4, and was used in the Example 17 without further purification.

^{1}H NMR δ (DMSO-d_6) 2.1 (3H, s); 3.1 (3H, s); 3.85 (2H, d); 4.3 (2H, d); 6.3 (1H, s); 7.15 (2H, d); 7.6 (2H, d); 7.75 (1H, s); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 19

5-[4-(2-(N-Methyl-N-[2-(5-phenyloxazolyl)]amino) ethoxy)benzyl]2,4-thiazolidinedione

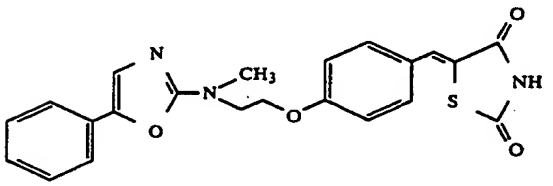


The title compound (m.p. 200° C., MeOH)) was prepared from 5-[4-(2-(N-methyl-N-[2-(5-phenyloxazolyl)-]amino ethoxy)benzylidene]-2,4-thiazolidinedione by a similar procedure to that described in Example 7.

^{1}H NMR δ (DMSO-d_6) 3.0–3.4 (2H, complex); 3.15 (3H, s); 3.8 (2H, t); 4.2 (2H, t); 4.85 (1H, complex); 6.9 (2H, d); 7.1–7.4 (6H, complex); 7.5 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 20

5-(4-[2-(N-Methyl-N-[2-(5-phenyloxazolyl)]amino) ethoxy]benzylidene)-2,4-thiazolidinedione

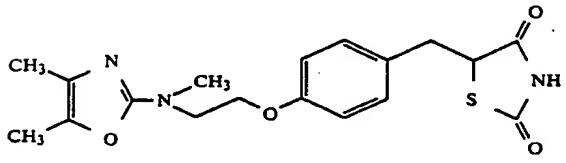


The title compound (m.p. 191° C.) was prepared from 4-[2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino) ethoxy]benzaldehyde by an analogous procedure to that described in Example 4.

^{1}H NMR δ (DMSO-d_6) 3.2 (3H, s); 3.8 (2H, t); 4.35 (2H, t); 7.1–7.7 10H, complex); 7.8 (1H, s); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 21

5-(4[2-(N-Methyl-N-[2-(4,5-dimethyloxazolyl)]amino) ethoxy]benzyl)-2,4-thiazolidinedione

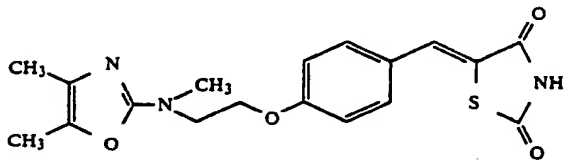


5-(4-[2-(N-Methyl-N-[2-(4,5-dimethyloxazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione (1.2 g) in dry 1,4-dioxan (100 ml) was reduced under hydrogen in the presence of 10% Palladium on charcoal (2.5 g) until hydrogen uptake ceased. The solution was filtered through diatomaceous earth, the filter pad was washed exhaustively with dioxan and the combined filtrates evaporated to dryness under vacuum. The title compound was obtained as a foam (m.p. 53°–54° C.) following chromatography on silica-gel in 1% methanol in dichloromethane.

^{1}H NMR δ (DMSO-d_6) 1.85 (3H, s); 2.05 (3H, s); 3.0 (3H, s); 3.0–3.4 (2H, complex); 3.65 (2H, t); 4.1 (2H, t); 4.85 (1H, complex); 6.85 (2H, d); 7.15 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 22

5-(4[2-(N-Methyl-N-2-(4,5-dimethyloxazoly)]amino)ethoxy]benzylidene-2,4-thiazolidinedione



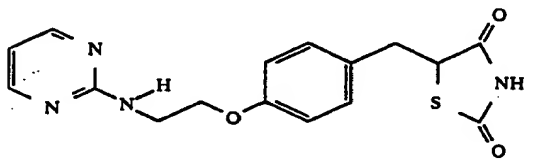
The title compound (softens at 149° C.) was prepared by a similar procedure to that described in Example 4.

^{1}H NMR δ (DMSO-d_6) 1.85 (3H, s); 2.05 (3H, s); 3.0 (3H, s); 3.7 (2H, t); 4.25 (2H, t); 7.1 (2H, d); 7.5 (2H, d); 7.75 (1H, s);

12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 23

5–4-(2-(2-Pyrimidinylamino)ethoxy)benzyl1-2,4-thiazolidinedione

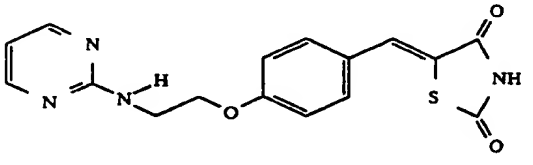


A mixture of 5-[4-(2-(2-pyrimidinylamino)ethoxy) benzylidene]-2,4-thiazolidinedione (3 g) and 10% palladium on charcoal (9 g) in DMF (70 ml) was stirred under a pressure of 200 psi of hydrogen until hydrogen uptake ceased. The mixture was filtered through diatomaceous earth, and the filter pad washed exhaustively with DMF. The combined filtrates were evaporated to dryness and the title compound (m.p. 173° C.) obtained following recrystallization from methanol.

^{1}H NMR δ (DMSO-d_6) 3.0–3.4 (2H, complex); 3.65 (2H, complex); 4.1 (2H, t); 4.85 (1H, complex); 6.6 (1H, t); 6.85 (2H, d); 7.15 (2H, d); 7.25 (1H, t, exchanges with D_2O); 8.3 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 24

5-[4-(2-(2-Pyrimidinylamino)ethoxy)benzylidenel-2,4-thiazolidinedione



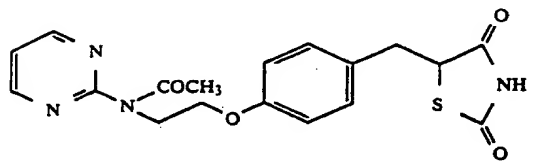
The title compound (m.p. 234° C.) was obtained from 4-[2-(2-pyrimidinylamino)ethoxy]benzaldehyde and 2,4-thiazolidindione, by an analogous procedure to that described in Example 6.

^{1}H NMR δ (DMSO-d_6) 3.65 (2H, complex); 4.2 (2H,t); 6.6 (1H, t); 7.0–7.6 (5H, complex, one proton

changes with D_2O); 7.7 (1H, s); 8.3 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 25

5-(4-[2-(N-Acetyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione

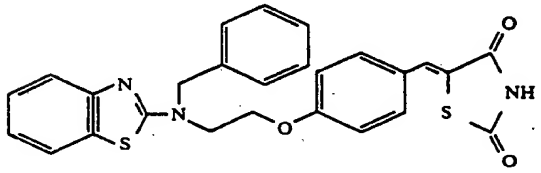


A stirred solution of 5-[4-(2-(2-pyrimidinylamino) ethoxy)benzyl]-2,4-thiazolidinedione (800mg) in acetic anhydride (15 ml) and 1,4-dioxan (5 ml) was boiled under reflux for 3 hours. After cooling, the mixture was added to water (300 ml), neutralized (sodium bicarbonate) and extracted with dichloromethane (3×200 ml). The organic extracts were washed with brine (100 ml), dried ($MgSO_4$), filtered and evaporated to dryness. Chromatography on silica-gel in dichloromethane of the residual oil afforded the title compound (m.p. 137° C.).

^1H NMR δ (DMSO-d_6) 2.3 (3H, s); 2.93.4 (2H, complex); 4.15 (2H,t); 4.35 (2H, t); 4.85 (1H, complex); 6.7 (2H,d); 7.1 (2H, d); 7.35 (1H, t); 8.8 (2H, d); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 26

5-(4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy) benzylidene)-2,4-thiazolidinedione

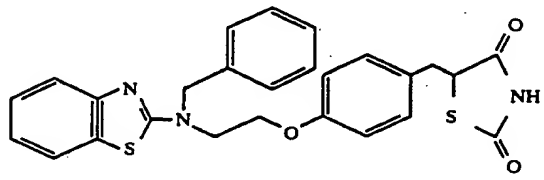


4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy) benzaldehyde (3 g) and 2,4-thiazolidinedione (1 g) were dissolved in toluene (200 ml) containing piperidine (0.2 ml) and benzoic acid (0.2 g) and heated to reflux for 4 h. in a Dean and Stark apparatus. On cooling, the solution was concentrated under vacuum to 50% of its volume and the title compound, which crystallised, was collected by filtration and dried in vacuo (m.p. 185°–188° C.). It was used in Example 27 without further purification.

^1H NMR δ (DMSO-d_6) 4.0 (2H, t); 4.4 (2H, t); 4.9 (2H, s); 7.1–7.9 (14H, complex); 12–13 (1H, broad s, exchanges with D_2O).

EXAMPLE 27

5-(4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy) benzyl)-2,4-thiazolidinedione

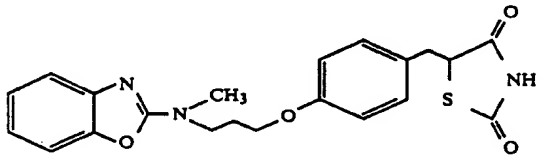


5-(4-(2-(N-(2-Benzothiazolyl)-N-benzylamino)ethoxy) benzylidene)-2,4-thiazolidinedione (2.4 g) in dioxan (150 ml) was hydrogenated in the presence of 10% palladium-charcoal (4.8 g) for 3 h. at room temperature and atmospheric pressure. A further portion of catalyst (2.4 g) was added and the hydrogenation continued for a total of 20 h. The mixture was filtered through diatomaceous earth and the solvent was evaporated. The residue was chromatographed on silica gel with 3% methanol-dichloromethane as eluant to afford the title compound as a foam, which collapsed at 78° C.

^1H NMR δ ($CDCl_3$) 3.1 (1H, dd); 3.4 (1H, dd); 4.0 (2H, t); 4.25 (2H, t); 4.5 (1H, dd); 4.9 (2H, s); 6.8–7.6 (13H, m); 8.3 (1H, broad s, exchanges with D_2O).

EXAMPLE 28

5-(4–3-(N-Methyl-N-(2-benzoxazolyl)amino)propoxy]-benzyl)-2,4-thiazolidinedione

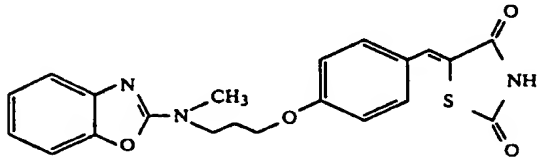


The title compound (m.p. 171°–3° C.; ethanol) was prepared from 5-(4-[3-(N-methyl-N-(2-benzoxazolyl-)amino)propoxy]benzylidene)-2–4-thiazolidinedione by a similar procedure to that described in Example 1.

^1H NMR δ) (DMSO - d_6) 2.0–2.35 (2H, complex); 2.9–3.6 (2H, complex); 3.2 (3H, s); 3.7 (2H, t); 4.2 (2H, t); 4.9 (1H, complex); 6.8–7.4 (8H, complex); 12–12.5 (1H, broad s, exchanges with D_2O).

EXAMPLE 29

4-[3-(N-Methyl-N-(2-benzoxazolyl)amino)propoxy]-benzylidene)-2,4-thiazolidinedione

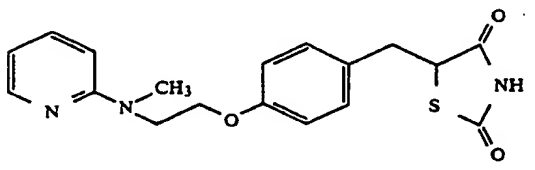


The title compound (m.p. 202°–204° C.) was prepared from 4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propoxy]benzaldehyde (5.3 g) and 2,4-thiazolidinedione (2.2 g) by a similar procedure to that described in Example 4.

^{1}H NMR δ (DMSO - d_6) 2.0–2.35 (2H, complex); 3.15 (3H, s); 3.7 (2H, t); 4.2 (2H, t); 7.0–7.7 (8H, complex); 7.8 (1H, s); 12.0 (1H, broad s, exchanges with D_2O).

EXAMPLE 30

5-(4–2-(N-Methyl-N-(2-ovridyl)amino)ethoxy1benzyl)2,4-thiazolidinedione

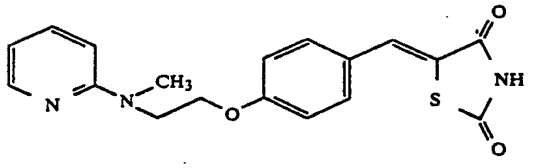


The title compound (m.p. 153°–5° C.; MeOH) was obtained from 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione by a similar procedure to that described in Example 1.

^{1}H NMR δ (DMSO - d_6) 2.9–3.4 (2H, complex); 3.1 (3H, s); 3.9 (2H, t); 4.15 (2H, t); 4.8 (1H, complex); 6.5–6.85 (2H, complex); 6.8 (2H, d); 7.2 (2H, d); 7.5 (1H, complex); 8.1 (1H, d); 12.05 (1H, broad s, exchanges with D_2O).

EXAMPLE 31

5-(4-[2-(N-Methyl-N-(2-cvridyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione

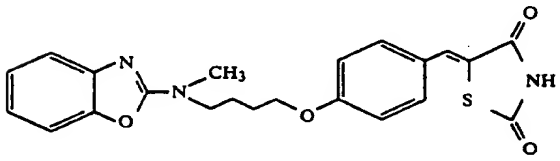


The title compound (m.p. 177°–9° C.) was obtained from 4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzaldehyde (3.2 g) and 2,4-thiazolidinedione (1.1 g) by a similar procedure to that described in Example 4.

^{1}H NMR δ (DMSO-D_2O) 3.1 (3H, s); 3.9 (2H, t); 4.2 (2H, t); 6.4–7.5 (7H, complex); 7.7 (1H, s); 8.1 (1H, d)

EXAMPLE 32

5-(4-[4-(N-Methyl-N-(2-benzoxazolyl)amino)butoxy]-benzylidene)-2,4-thiazolidinedione.

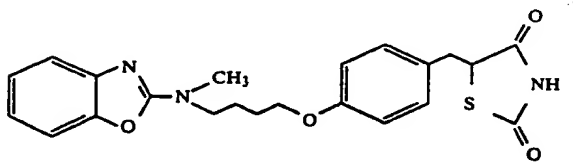


The title compound (m.p. 168° C.; was prepared from 4-[4-(N-methyl-N-(2-benzoxazolyl)amino)butoxy]benzaldehyde (3.5 g) and 2,4-thiazolidinedione (1.4 g) by a similar procedure to that described in Example 4.

^{1}H NMR δ DMSO-$d_6$1.70 (4H, complex); 3.10 (3H, s); 3.25 (1H, exchanges with D_2O); 3.50 (2H, complex); 4.05 (2H, complex); 6.90–7.60 (8H, complex); 7.70 (1H, s).

EXAMPLE 33

5(4-[4-(N-Methyl-N-(2-benzoxazolyl)amino)butoxy]-benzyl)-2,4-thiazolidinedione

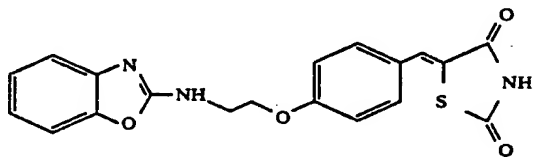


The title compound (m.p. 112° C., ethanol-hexane) was prepared from 5-(4-[4-(N-methyl-N-(2-benzoxazolyl-)amino)butoxy]benzylidene)-2,4-thiazolidinedione by a similar procedure to that described in Example 1.

^{1}H NMR δ $CDCl_3$1.85 (4H, complex); 3.10 (1H, complex); 3.15 (3H,s); 3.40 (1H,dd); 3.60 (2H,t); 4.00 (2H,t); 4.50 (1H,dd); 6.80–7.40 (8H, complex); 9.30 (1H, br, exchanges with D_2O).

EXAMPLE 34

5-(4-[2-(N-(2-Benzoxazolyl)amino)ethoxy]benzylidene)2,4-thiazolidinedione

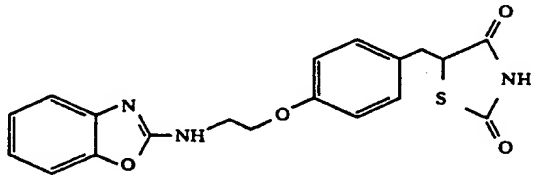


The title compound (m.p. 242°–5° C.) was prepared from 4-[2-(N-(2-benzoxazolyl)amino)ethoxy]benzaldehyde (5.18 g) and 2,4-thiazolidinedione (2.36 g) by a similar procedure to that described in Example 4.

^{1}H NMR δ DMSO-$d_6$3.80 (2H,t); 4.35 (2H,t); 7.00–8.00 (9H, complex); 8.20 (1H, br, exchanges with D_2O); 13.5 (1H, br, exchanges with D_2O).

EXAMPLE 35

5-(4-[2-(N-(2-Benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione

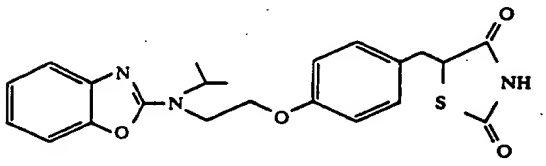


The title compound (m.p. 202°–3° C.; dichloromethane) was prepared from 5-(4-[2-(N-(2-benzoxazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione (6.1 g) by a similar procedure to that described in Example 1.

^{1}H NMR δ DMSO-$d_6$3.10 (1H,dd); 3.30 (1H,dd) 3.70 (2H, complex); 4.15 (2H,t); 4.85 (1H,dd); 6.80–7.50 (8H, complex); 8.15 (1H, complex; exchanges with D_2O); 12.00 (1H, br, exchanges with D_2O).

EXAMPLE 36

5-(4[2-(N-Isopropyl-N-(2-benzoxazolyl)amino)ethoxy]-benzyl)-2,4-thiazolidinedione.



Sodium hydride (60% dispersion in mineral oil, 0.93 g) was added portionwise to a stirred solution of 5-(4-hydroxybenzyl)-2,4-thiazolidinedione (2.45 g in dry DMF (50 ml)) at room temperature under a nitrogen atmosphere. The mixture was stirred for 1 hour prior to the addition of a solution of 2-[N-isopropyl-N-(2-benzoxazolyl)amino]ethanol methanesulphonyl ester (3.3 g) in dry DMF (60 ml). After stirring at room temperature for a further hour, the mixture was heated at 80° C. for 21 hours, then cooled, diluted with water (1l) and acidified to pH 6.5 with hydrochloric acid. The resulting suspension was extracted with ethyl acetate (2×500 ml), and the combined ethyl acetate layers washed with water (3×1l), brine (1l), dried ($MgSO_4$) and evaporated. The residual oil was chromatographed on silica gel with 1.5% methanol-dichloromethane as solvent to afford the title compound as a foam (m.p. 66° C.).

^1H NMR δ ($CDCl_3$) 1.35 (6H,d); 3.1 (1H, dd); 3.4 (1H, dd); 3.8 (2H,t); 4.15 (2H, complex); 4.35–4.65 (2H, complex); 6.85–7.4 (8H, complex); and 9.15 (1H, broad s,; exchanges With D_2O)

DEMONSTRATION OF EFFICACY OF COMPOUNDS

Obese Mice, Oral Glucose Tolerance Test

C57bl/6 obese (ob/ob) mice were fed on powdered oxoid diet. After at least one week, the mice continued on a powdered oxoid diet or were fed powdered oxoid diet containing the test compound. After 8 days on the supplemented diet all of the mice were fasted for 5 hours prior to receiving an oral load of glucose (3 g/kg). Blood samples for glucose analysis were taken 0, 45, 90 and 135 minutes after glucose administration and the results appear below as the percentage reduction in area under the blood glucose curve where test compound treated groups are compared with the control groups. 7 mice were used for each treatment.

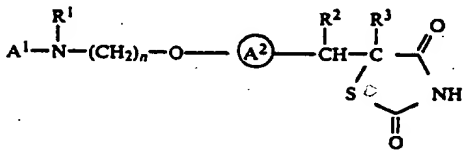
EXAMPLE NO:	LEVEL IN DIET (μmol kg^{-1} of DIET)	% REDUCTION IN AREA UNDER BLOOD GLUCOSE CURVE
1	100	51
2	300	30
3	10	39
4	300	30
5	100	40
7	50	47
9	100	58
11	100	34
13	100	37
15	100	39
17	100	34
19	30	22
21	30	33
24	30	15
25	30	19
27	300	56
29	300	32
33	300	25
35	100	44
36	100	20

Toxicology

No toxicological effects were indicated for any of the compounds of the invention in any of the abovementioned tests.

I claim:

1. A compound of formula (I):



(I)

or a tautomeric form thereof and/or pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein:

A^1 represents a substituted or unsubstituted, single ring aromatic heterocyclyl group having 4 to 7 ring atoms and comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen, the substituents for the heterocyclyl group being up to 4 substituents selected from the group consisting of: C_{1-12}-alkyl, C_{1-12}-alkoxy, aryl and halogen or any two substituents on adjcent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted;

R^1 represents a hydrogen atom, a C_{1-12}-alkyl group, a C_{1-6} alkylcarbonyl group, an aryl-C_{1-12}-alkyl group the aryl moiety being substituted or unsubstituted, or a substituted or unsubstituted aryl group;

any aryl group being phenyl or naphthyl optionally substituted with up to five groups selected from halogen, C_{1-12}-alkyl, phenyl, C_{1-12}-alkoxy, halo-C_{1-12}-alkyl, hydroxy, amino, nitro, carboxy, C_{1-12}-alkylcarbonyloxy, or a C_{1-12}-alkylcarbonyl group;

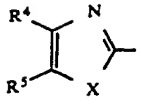
Rhu 2 and R^3 each represent hydrogen, or R^2 and R^3 together represent a bond;

A^2 represents a benzene ring having three optional substituents which may be selected from halogen, substituted or unsubstituted alkyl or alkoxy; substituents for the alkyl group being selected from the groups consisting of halogen, C_{1-12}-alkyl, phenyl, C_{1-12}-alkoxy, halo-C_{1-12}-alkyl, hydroxy, amino, nitro, carboxy, C_{1-12}-alkoxycarbonyl, C_{1-12}-alkoxycarbonyl-C_{1-12}-alkyl, C_{1-12}-alkylcarbonyloxy, or C_{1-12}-alkylcarbonyl; and

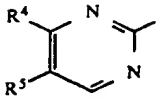
n represents an integer in the range of from 2 to 6.

2. A compound according to claim 1, wherein A^1 represents a substituted or unsubstituted, single or fused ring aromatic heterocyclyl group comprising up to 4 hetero atoms in the ring selected from oxygen, sulphur or nitrogen.

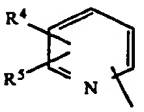
3. A compound according to claim 1, wherein A^1 represents a moiety of formula (a), (b) or (c):



(a)



(b)



(c)

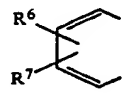
wherein:

R^4 and R^5 each independently represents a hydrogen atom, an alkyl group or a substituted or unsubstituted aryl group or when R^4 and R^5 are each attached to a carbon atom, then R^4 and R^5 together with the carbon atoms to which they are attached form a benzene ring wherein each carbon atom represented by R^4 and R^5 together may be substituted or unsubstituted; and in the moiety of formula (a)

X represents oxygen or sulphur.

4. A compound according to claim 3, wherein R^4 and R^5 each independently represent hydrogen, alkyl or a substituted or unsubstituted phenyl group.

5. A compound according to claim 3, wherein R^4 and R^5 together represent a moiety of formula (d):



(d)

wherein R^6 and R^7 each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

6. A compound according to claim 5, wherein R^6 and R^7 both represent hydrogen.

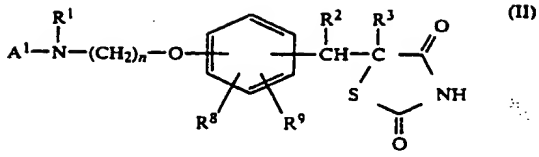
7. A compound according to claim 1, wherein A^2 represents a moiety of formula (e):

(e)

wherein R^8 and R^9 each independently represent hydrogen, halogen, suostituted or unsubstituted alkyl or alkoxy.

8. A compound according to claim 7, wherein R^8 and R^9 each represent hydrogen.

9. A compound according to claim 1, of formula (II):



(II)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein A^1, R^1, R^2, R^3 and n are as defined in relation to formula (I) in claim 1 and R^8 and R^9 are as defined in relation to formula (e) in claim 7.

10. A compound according to claim 1, wherein n represents an integer 2 or 3.

11. A compound according to claim 1, wherein R^1 represents a methyl group.

12. A compound according to claim 1, selected from the group consisting of:

5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]-benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-pyrimidinyl)amino)ethoxy]-benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-pyrimidinyl)amino)ethoxy]-benzylidene)-2,4-thiazolidinedione;

5-(4-(2-(N-methyl-N-[2-(4,5-dimethylthiazolyl)-]amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4,5-dimethylthiazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-thiazolyl)amino)ethoxy]benzyl) -2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-thiazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-[4-(2-(N-methyl-N-(2-(4-phenylthiazolyl))amino) ethoxy)benzyl]-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-(2-(4-phenylthiazolyl))amino) ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)-]amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)-]amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

b 5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)-]amino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]amino) ethoxy]benzylidene)-2,4-thiazolidinedione;

5-[4-(2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino) ethoxy)benzyl]-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino) ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4,5-dimethyloxazolyl)-]amino) ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-methyl-N-[2-(4,5-dimethyloxazolyl)-]amino)ethoxy]benzylidene)-2,4-thiazolidinedione;

5-[4-(2-(2-pyrimidinylamino)ethoxy)benzyl]-2,4-thiazolidinedione;

5-[4-(2-(2-pyrimidinylamino)ethoxy)benzylidene]-2,4-thiazolidinedione;
5-(4-[2-(N-acetyl-N-(2-pyrimidinyl)amino)ethoxy]-benzyl) -2,4-thiazolidinedione;
5-(4-(2-(N-(2-benzothiazolyl)-N-benzylamino)e-thoxy) benzylidene)-2,4-thiazolidinedione;
5-(4-(2-(N-(2-benzothiazolyl)-N-benzylamino)e-thoxy) benzyl)-2,4-thiazolidinedione;
5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propox-y]benzyl)-2,4-thiazolidinedione;
5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propox-y]benzy lidene)-2,4-thiazolidinedione;
5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]ben-zyl)-2,4-thiazolidinedione;
5-(4 [2-(N-methyl-N-(2-pyridyl)amino)ethoxy]ben-zylidene)-2,4-thiazolidinedione;
5-(4-[4-(N-methyl-N-(2-benzoxazolyl)amino)butoxy]-benzylidene)-2,4-thiazolidinedione;
5-(4-[4-(N-methyl-N-(2-benzoxazolyl)amino)butoxy]-benzyl)-2,4-thiazolidinedione;
5-(4-[2-(N-(2-benzoxazolyl)amino)ethoxy]ben-zylidene)2,4-thiazolidinedione;
5-(4-[2-(N-(2-benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; and
5-(4-[2-(N-isopropyl-N-(2-benzoxazolyl)amino)e-thoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

13. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

14. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-(2-benzothiazolyl)amino)ethoxy]ben-zylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

15. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

16. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-(2-benzoxazolyl)amino)ethoxy]ben-zylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

17. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

18. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-(2-pyrimidinyl)amino)ethoxy]ben-zylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

19. A compound according to claim 1 being 5-(4-(2-(N-methyl-N-[2-(4,5-dimethylthiazolyl)]amino)ethoxy]-benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

20. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-[2-(4,5-dimethylthiazolyl)]amino)ethoxy]-benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

21. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-(2-thiazolyl)amino)ethoxy]benzyl)2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

22. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-(2-thiazolyl)amino)ethxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

23. A compound according to claim 1 being 5-[4-(2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy)ben-zyl]-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and-/or a pharmaceutically acceptable solvate thereof.

24. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-(2-(4-phenylthiazolyl))amino)ethoxy]ben-zylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof

25. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)]amino)e-thoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

26. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-[2-(4-phenyl-5-methylthiazolyl)]amino)e-thoxy]benzylidene)-2,4-thiazolidinedine; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof

27. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]amino)e-thoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

28. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-[2-(4-methyl-5-phenylthiazolyl)]amino)e-thoxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

29. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]amino)ethoxy]ben-zyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and-/or a pharmaceutically acceptable solvate thereof.

30. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-[2-(4-methylthiazolyl)]amino)ethoxy]ben-zylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

31. A compound according to claim 1 being 5-[4-(2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy)ben-zyl]-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and-/or a pharmaceutically acceptable solvate thereof.

32. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-[2-(5-phenyloxazolyl)]amino)ethoxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

33. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-[2-(4,5-dimethyloxazolyl)]amino)ethoxy]-benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

34. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-[2-(4,5-dimethyloxazolyl)]amino)ethoxy]-benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

35. A compound according to claim 1 being 5-[4-(2-(2-pyrimidinylamino)ethoxy)benzyl]-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

36. A compound according to claim 1 being 5-[4-(2-(2-pyrimidinylamino)ethoxy)benzylidene]-2,4thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

37. A compound according to claim 1 being 5-(4-[2-(N-acetyl-N-(2-pyrimidinyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically accepta,ble solvate thereof.

38. A compound according to claim 1 being 5-(4-(2-(N-(2-benzothiazolyl)-N-benzylamino)ethoxy)benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

39. A compound according to claim 1 being 5-(4-(2-(N-(2-benzothiazolyl)-N-benzylamino)ethoxy)benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

40. A compound according to claim 1 being 5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

41. A compound according to claim 1 being 5-(4-[3-(N-methyl-N-(2-benzoxazolyl)amino)propoxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

42. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl)2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

43. A compound according to claim 1 being 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

44. A compound according to claim 1 being 5-(4-[4-(N-methyl-N-(2-benzoxazolyl)amino)butoxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

45. A compound according to claim 1 being 5-(4-[4-(N-methyl-N-(2-benzoxazolyl)amino)butoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

46. A compound according to claim 1 being 5-(4-[2-(N-(2-benzoxazolyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

47. A compound according to claim 1 being 5-(4-[2-(N-(2-benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

48. A compound according to claim 1 being 5-(4-[2-(N-isopropyl-N-(2-benzoxazolyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and-/or a pharmaceutically acceptable solvate thereof.

49. A compound according to claim 1, wherein A^1 represents a substituted or unsubstituted single ring aromatic heterocyclyl group having 5 or 6 ring atoms.

50. A compound according to claim 1, wherein A^1 represents a substituted or unsubstituted thiazolyl, oxazolyl, pyridyl or pyrimidinyl group.

51. A compound according to claim 1, wherein A^1 represents a substituted or unsubstituted oxazolyl, pyridyl or pyrimidinyl group.

52. A pharmaceutical composition comprising a non-toxic effective amount of the compound of formula (I) according to claim 1, or a tautomeric form thereof or a pharmaceutically acceptable salt thereof or pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

53. A method for the treatment and/or prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a hyperglycaemic human or non-human mammal in need thereof.

54. A method for the treatment of hyperlipidaemia in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I) according to claim 1, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a hyperlipidaemic human or non-human mammal in need thereof.

55. A method for the treatmetn and/or prophylaxis of diseases selected from the group consisting of hyperglycaemia and hyperlipidaemia in a human or a non-human mammal which comprises administering to said human or non-human mammal in need thereof, an effective, non-toxic, amount of a compound of formula (I) according to claim 1, or a tautomeric form thereof and-/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof.

* * * * *

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
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[redacted]

ATTACHMENT B

000124

m75n5

MASTER DATA CENTER, INC.
29100 NORTHWESTERN HIGHWAY
SUITE 300
SOUTHFIELD MI 48034-1095

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,002,953	183	930	----	07/457,272	03/26/91	12/27/89	04	NO	PAID

ITM NBR	ATTY DKT NUMBER
1	0132138A

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
COMMISIONER OF PATENTS AND TRADEMARKS, BOX M. FEE, WASHINGTON, D.C. 20231

PTOL-439 (REV. 11-97)

ATTACHMENT C

SmithKline Beecham
Pharmaceuticals

MEMORANDUM

TO: YURIY STERCHO, (UW2220)

FROM: YVETTE K CLARK (FP1145)
DOCUMENT REQUEST COORDINATOR

SUBJECT: DOCUMENT REQUEST - AVANDIA PATENT TERM EXTENSION

DATE: 07/19/99

CC: C. KAHN (UP4340); D. ROBERTS (FP1010); S. SHAPOWAL (UP3440); M. STUMPO (UW2220); S. VENETIANER (UW2220); M. WHITMAN (UP4340)

In response to your 7/8/1999 request, enclosed please find a report of the Avandia regulatory documents on file with SmithKline Beecham's US Regulatory Affairs Archives. The report is sorted in chronological order and includes those documents issued from 12/01/1992 through 05/31/1999. This reports includes:

⇒ **Submissions to FDA**
⇒ **Correspondence from FDA**
⇒ **Internal Communications which document phone conversations and meetings with the FDA**

These documents have been provided to you for inclusion in the Patent Term Extension Application for Avandia. If you have any questions regarding this report, I can be reached at 8-282-7517.

DOCUMENT LISTING
Product: AVANDIA
12-01-1992 to 05-31-1999

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
MEMO	AVANDIA EPRISTERIDE SKF-097426 SKF-106686	General	12/28/1992		SUMMARY OF DISCUSSIONS DURING TRIP TO GREAT BURGH.
MEMO	AVANDIA	GENERAL	12/28/1992		DOCUMENTS A TRIP TO GREAT BURGH TO ADDRESS KEY ELEMENTS OF THE EPRISTERIDE DEVELOPMENT STRATEGY.
MEMO	AVANDIA	General	04/05/1993		ATTACHED DRAFT TIMELINE FOR BRL-49653.
SUB	AVANDIA	IND-43468	09/22/1993	INITIAL IND	INITIAL INVESTIGATIONAL NEW DRUG APPLICATION. THE PROPOSED PRIMARY INDICATION IS FOR THE CONTROL OF PLASMA GLUCOSE CONCENTRATIONS IN PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS.
CFF	AVANDIA	IND-43468	09/29/1993		FDA ACKNOWLEDGED RECEIPT ON 9/23/93 OF IND APPLICATION DATED 9/22/93 AND ASSIGNED THE APPLICATION NUMBER, IND-43468.
SUB	AVANDIA	IND-43468-S-001	10/22/1993		SUBMITTED IND SAFETY REPORT PERTAINING TO DEATHS IN 4/20 FEMALE RATS IN HIGH DOSE (40 MG/KG) GROUP AT WEEK 16 OF SB"S ON-GOING SIX MONTH TOXICOLOGY STUDY WITH BRL-49653C.
MEMO	AVANDIA	IND-43468	10/26/1993		DR. JORDAN, SUPERVISORY PHARMACOLOGY REVIEWER, INDICATED AFTER REVIEWING THE ADVANCE COPY OF THE SAFETY REPORT FOR BRL-49653C, THAT HE HAD NO PROBLEMS WITH SB PROCEEDING WITH THE SINGLE DOSE VOLUNTEER STUDY.
CFF	AVANDIA	IND-43468	12/06/1993		FDA HAVE COMPLETED THEIR EVALUATION OF THE 10/22/93 SAFETY REPORT AND CONCLUDED THE SINGLE-DOSE SAFETY STUDY MAY PROCEED. FDA ALSO COMMENTED ON THE PHARMACOLOGY PORTION OF THE INITIAL SUBMISSION.
SUB	AVANDIA	IND-43468-S-002	12/09/1993		INITIAL REPORTS OF VENTRICULAR ARRHYTHMIA THAT OCCURRED IN A SMITHLINE BEECHAM SPONSORED IND STUDY PN-001, AE-93004965-1 AND AE-93004972-1.
SUB	AVANDIA	IND-43468-S-003	01/13/1994		SUBMITED UPDATED REPORTS OF VENTRICULAR ARHYTHMIA THAT OCCURRED IN IND STUDY PN-001: AE-93004965-1 AND AE-93004972-1, ORIGINALLY REPORTED 12/9/93.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
MEMO	AVANDIA	IND-43468	01/13/1994		QUESTIONS CONCERNING LETTER DATED 12/6/93 FROM FDA. // DR. JOHN GUERIGUIAN, MEDICAL OFFICER, REQUESTED PHARMACOKINETIC DATA FROM SB"S NEXT PHASE-1 STUDY.
SUB	AVANDIA	IND-43468-S-004	02/04/1994		AMENDMENT 1 TO PN-001. // REMOVED REQUIREMENT FOR BED REST AND HOURLY TESTING OF SUBJECTS FOR ORTHOSTASIS FOR INCREASES IN HEART RATE >15 BPM.
SUB	AVANDIA	IND-43468-S-005	02/21/1994		RESPONSE TO FDA REQUEST OF 12/6/93 FOR COMMENTS ON THE PHARMACOLOGY PORTION OF THE INITIAL IND.
SUB	AVANDIA	IND-43468-S-006	02/25/1994		PHARMACOKINETIC DATA FROM SB"S PHASE-1 STUDY (ATTACHMENT 1) AND THE PHARMACOKINETIC DATA COLLECTED IN VOLUNTEERS IN THE INITIAL STUDY (ATTACHMENT 2). ALSO ENCLOSED IS THE NEXT STUDY, PN-004, AN OPEN LABEL, TWO WAY CROSSOVER STUDY OF THE EFFECT OF FOOD ON THE PHARMACOKINETICS OF THE DRUG, AS WELL AS DOCUMENTATION FOR THE PRINCIPAL INVESTIGATOR, MARTIN FREED, M.D., TO CONDUCT PN-004 (ATTACHMENT 3).
CFF	AVANDIA	IND-43468	04/05/1994		(FAX) FDA INFORMED SB THAT PN-49653-001 MAY PROCEED AND OFFERED COMMENTS TO FACILITATE THE DEVELOPMENT OF THE DRUG. // ATTACHED CHEMIST"S COMMENTS.
MEMO	AVANDIA	IND-43468	04/05/1994		(FAX) ATTACHED FAX FROM FDA DOCUMENTED THE RESULTS OF THE FDA MEDICAL AND CHEMISTRY REVIEW. MEDICAL REVIEWER"S COMMENTS WERE ALREADY RECEIVED IN A CALL 1/13/94.
SUB	AVANDIA	IND-43468-S-007	04/05/1994		SUBMITTED INITIAL MULTIPLE DOSE STUDY, PN-002, A 10 DAY REPEAT DOSE STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS IN OBESE, INSULIN RESISTANT OR MILDLY DIABETIC SUBJECTS.
MEMO	AVANDIA	IND-43468	04/22/1994		IMPOSITION OF CLINICAL HOLD. // JOHN SHORT INFORMED SB THAT DR. SOBEL HAD INFORMED HIM TO PLACE FURTHER STUDIES ON CLINICAL HOLD. // ARRHYTHMIAS, INCREASED HEART WEIGHT IN PATHTOX STUDY.
MEMO	AVANDIA	IND-43468	04/25/1994		IMPOSITION OF CLINICAL HOLD. // SOLOMON SOBEL INDICATED THE NEED FOR A MEETING BEFORE PROCEEDING WITH FURTHER STUDIES. // ELECTROPHYSIOLOGY, HOLTER MONITORING.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
CFF	AVANDIA	IND-43468	05/02/1994		FDA CONFIRMED THE TELEPHONE CONVERSATION OF 04/22/94 BETWEEN SB AND JOHN SHORT OF THE FDA REGARDING FDA"S REQUEST THAT SB CEASE CLINICAL STUDIES UNDER THIS IND DUE TO THE OCCURRENCE OF TWO CASES OF VENTRICULAR ARRHYTHMIAS IN HUMANS. // FDA ALSO CITED A PRECLINICAL STUDY RESULTING IN ENLARGED HEARTS IN A DOG. FDA SUGGESTED A MEETING ON THIS ISSUE.
SUB	AVANDIA	IND-43468-S-008	05/06/1994	RESPONSE TO CLINICAL HOLD	SUBMITTED MATERIALS, WHICH INCLUDE A LIST OF SB ATTENDEES, A PROPOSED AGENDA FOR SB"S PRESENTATION, INFORMATION RELATING TO PN-001, INFORMATION RELATING TO THE SPONTANEOUS INCIDENCE OF ARRHYTHMIAS AND INFORMATION FROM PRECLINICAL STUDIES, FOR THE FDA TO REVIEW BEFORE THE 5/12/1994 MEETING.
MEMO	AVANDIA	IND-43468	05/09/1994		BRL-49653C CLINICAL HOLD RESPONSE. // CHARLES GANLEY INDICATED HE FOUND NO DATA IN THE PRE-MEETING PACKAGE WHICH WOULD RULE OUT A TREATMENT EFFECT WITH CERTAINTY, BUT SB SHOULD BE ABLE TO PROCEED WITH THE MULTIDOSE TRIAL WITH AGREED MONITORING PROCEDURES. // HOLTER MONITORING, ECG MONITORING
MEMO	AVANDIA	IND-43468	05/10/1994		CLINICAL HOLD MEETING. // SB INFORMED JOHN SHORT THAT THE RE-SORTED PLACEBO PERIOD VITAL SIGN DATA AND THE ECG INTERVAL DATA WOULD BE FAXED TO HIM. MR. SHORT REQUESTED 3 ADDITIONAL COPIES OF THE MEETING PACKAGE.
MEMO	AVANDIA	IND-43468	05/10/1994		CHARLES GANLEY REQUESTED SUMMARY DATA FROM CARDIAC MONITORING IN STUDY PN-001. // HOLTER MONITORING, ECG MONITORING.
SUB	AVANDIA	IND-43468-S-009	05/19/1994		SUBMITTED SB"S VERSION OF THE MINUTES OF THE 5/12/94 MEETING TO RESOLVE CLINICAL HOLD ON THE IND.
MEMO	AVANDIA	IND-43468	05/27/1994		SB VERSION OF THE SB - FDA MEETING OF 5/12/94 CONCERNING BRL-49653C IND-43468.
MEMO	AVANDIA	IND-43468	06/07/1994		ATTACHED FAX FROM THE FDA CONTAINS THE METABOLISM AND ENDOCRINE DIVISON VERSION OF THE 5/12/94 MEETING CONCERNING THE CLINICAL HOLD ON IND-43468.
SUB	AVANDIA	IND-43468-S-010	06/14/1994		SUBMITTED AMENDMENT 1 TO PN-002 WHICH INCORPORATES CHANGES DISCUSSED AND AGREED TO AT THE 5/12/94 MEETING, WHICH INCLUDES CONTINUOUS HOLTER MONITORING OF SUBJECTS ON DAYS 1, 2, 9 AND 10. ALSO SUBMITTED DOCUMENTATION FOR THE PRINCIPAL INVESTIGATOR, JERRY HERRON, TO CONDUCT PN-002.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-011	06/17/1994		SUBMITTED 1) VITAL SIGN DATA FROM PN-001 SORTED FOR PLACEBO ADMINISTRATION AND 2) TABULATED PR AND QTC INTERVAL DATA FROM ECG"S PERFORMED IN PN-001.
SUB	AVANDIA	IND-43468-S-012	06/27/1994		SUBMITTED A NEW STUDY, PN-013, "A STUDY OF THE EFFECT OF AGE ON THE PHARMACOKINETICS OF BRL 49653 IN HEALTHY VOLUNTEERS". DOCUMENTATION FOR THE PRINCIPAL INVESTIGATOR, MARTIN FREED, OF PHILADELPHIA, PA., IS ALSO ENCLOSED.
CFF	AVANDIA	IND-43468	07/22/1994		FDA LIFTED THE CLINICAL HOLD AND PN-002 MAY PROCEED.
MEMO	AVANDIA	IND-43468	07/25/1994		INTERNAL DISTRIBUTION OF FDA LETTER DATED 7/22/94 AND RECEIVED BY SB ON 7/25/94 CONFIRMING THAT THE CLINICAL HOLD PLACED ON IND-43468 WAS LIFTED AS OF 5/12/94.
SUB	AVANDIA	IND-43468-S-013	07/25/1994		SUBMITTED NEW STUDY PN-016, "EVALUATION OF THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SINGLE RISING ORAL DOSES OF 5, 10, 15, AND 20 MG BRL-49653 IN HEALTHY MALE VOLUNTEERS", AS WELL AS DOCUMENTATION FOR THE PRINCIPAL INVESTIGATOR, MARTIN FREED, PHILADELPHIA, PA.
SUB	AVANDIA	IND-43468-S-014	10/14/1994		SUBMITTED AN INFORMATION AMENDMENT CONTAINING THE RESULTS OF 26 WEEK ORAL REPEAT DOSE TOXICOLOGY STUDIES CONDUCTED IN RATS AND DOGS: SB REPORT NUMBERS TF-1023-BRL-049653-1 AND TF-1022-BRL-049653-1.
SUB	AVANDIA	IND-43468-S-015	10/21/1994		SUBMITTED REPLIES TO FIVE COMMENTS ON THE CHEMISTRY PORTION OF THE INITIAL IND, SUBMITTED 9/22/94. ISSUES CONCERN 1) THE IMS USED IN DRUG SYNTHESIS, 2) THE AMOUNT OF SB-211656 FOR BATCH 34490-131, 3) THE STABILITY OF THE ACTIVE DRUG, 4) UNDER WHICH IN VITRO CONDITIONS THERE IS ENANTIOMERIC CONVERSION, AND 5) THE COMPENDIAL REQUIREMENTS OF THE INACTIVE INGREDIENTS.
SUB	AVANDIA	IND-43468-S-016	11/08/1994		SUBMITTED AN INFORMATION AMENDMENT CONTAINING RESULTS FROM EIGHT PRECLINICAL STUDIES CONDUCTED IN RATS AND DOGS TO OBTAIN PHARMACOKINETIC DATA AND DATA RELATING TO MYOCARDIAL HYPERTROPHY.
SUB	AVANDIA	IND-43468-S-017	11/11/1994		SUBMITTED SAFETY AND PHARMACOKINETIC DATA FROM PHASE-1 STUDIES, PN-001, PN-002, PN-004, PN-013 AND PN-016 AND A SYNOPSIS OF PHASE-2 STUDY, PN-006. SB REQUESTED COMMENTS FROM THE FDA ON THE PROPOSED DESIGN OF THE INITIAL PATIENT TRIAL STUDY, PN-006, A 12 WEEK PHASE-2 DOSE RANGING EFFICACY STUDY TO BE CONDUCTED IN NON-INSULIN DEPENDENT DIABETIC PATIENTS.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
MEMO	AVANDIA	IND-43468	12/06/1994		REQUEST FOR COMMENT, PHASE 2A PN-006 // 12/6/94 CONVERSATION WITH JOHN GUERIGUIAN, IN WHICH HE INDICATED THAT THE STUDY DESIGN OF PN-006 LOOKED RATIONALE. JOHN SHORT CALLED LATER IN THE DAY REGARDING THE STATUS OF THE CARDIO-RENAL REVIEW OF THIS SUBMISSION. // SAFETY / KINETIC; HOLTER
MEMO	AVANDIA	IND-43468	12/09/1994		BRL-49653C HOLTER DATA REVIEW // 12/9/94 PHONE CONVERSATION WITH DR. CHARLES GANLEY CONCERNING THE HOLTER DATA FROM PHASE-1 STUDIES PN-002 AND PN-016, WHICH WAS SUBMITTED IN EARLY 11//94.
MEMO	AVANDIA	IND-43468	12/14/1994		DISCUSSION OF PRECLINICAL PHARMACOLOGY DATA // 12/12/94 PHONE CONVERSATION WITH HERMAN RHEE CONCERNING PHASE-2 STUDY, PN-006. // MYOCARDIAL HYPERTROPHY
MEMO	AVANDIA	IND-43468	12/16/1994		BRL-49653C HOLTER DATA REVIEW // 12/16/94 PHONE CONVERSATION IN WHICH CHARLES GANLEY CONFIRMED THAT HE REVIEWED THE HOLTER DATA AND HAD NO PROBLEMS WITH SB PROCEEDING WITH PROPOSED 12 WEEK PATIENT STUDY.
SUB	AVANDIA	IND-43468-S-018	12/23/1994		ANNUAL REPORT FROM 10/23/93 TO 9/22/94 INCLUDING INDIVIDUAL STUDY INFORMATION; SUMMARY INFORMATION; GENERAL INVESTIGATIONAL PLAN; AND INVESTIGATOR BROCHURE.
SUB	AVANDIA	IND-43468-S-019	01/06/1995		SUBMITTED DRAFT PROTOCOLS FOR THE MOUSE AND RAT CARCINOGENICITY STUDIES FOR BRL-49653C, AS REQUESTED BY THE FDA IN THEIR 12/6/93 LETTER. A RATIONALE FOR THE SELECTION OF DOSES IS PROVIDED WITHIN EACH STUDY PROTOCOL.
MEMO	AVANDIA	IND-43468	01/20/1995		REQUEST FOR COMMENT, CARCINOGENICITY STUDY PROTOCOLS // 1/19/95 CONVERSATION IN WHICH HERMAN RHEE REQUESTED ADDITIONAL INFORMATION FROM YET TO BE REPORTED DOSE RANGING AND CLINICAL STUDIES CITED TO SUPPORT THE PROPOSED CARCINOGENICITY STUDY DOSES.
SUB	AVANDIA	IND-43468-S-020	01/24/1995		SUBMITTED ADDITIONAL INFORMATION FROM YET-TO-BE REPORTED DOSE-RANGING AND CLINICAL STUDIES CITED TO SUPPORT THE PROPOSED DOSES FOR THE RODENT CARCINOGENICITY STUDIES. THIS SUBMISSION WAS MADE IN RESPONSE TO DR. RHEE"S REQUEST OF 1/19/95.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-021	01/30/1995		SUBMITTED PN-006, ENTITLED, "A 12-WEEK, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE RESPONSE STUDY ASSESSING THE SAFETY, TOLERABILITY, AND EFFICACY OF BRL-49653C IN PATIENTS WITH NON INSULIN DEPENDENT DIABETES MELLITUS (NIDDM)." DOCUMENTATION FOR THE FIRST INVESTIGATOR, W. THOMAS GARLAND, TO CONDUCT PN-006 IS ENCLOSED. DRUG SUBSTANCE AND DRUG PRODUCT CHEMISTRY, MANUFACTURING AND CONTROL INFORMATION IS ALSO ENCLOSED.
MEMO	AVANDIA	IND-43468	01/30/1995		FURTHER QUESTIONS ON DRAFT RODENT CARCINOGENICITY PROTOCOLS // 1/26/95 PHONE CONVERSATION IN WHICH HERMAN RHEE REQUESTED ADDITIONAL PHARMACOKINETIC / METABOLISM INFORMATION WHICH SUPPORTS THE PROPOSED HIGH DOSE SELECTION BASED ON PHARMACOKINETIC ENDPOINTS.
SUB	AVANDIA	IND-43468-S-022	02/02/1995		SUBMITTED A NEW PHASE-1 STUDY, PN-014, ENTITLED, "A STUDY TO DETERMINE THE EFFECT OF BRL-49653C ON THE STEADY-STATE PHARMACODYNAMICS AND PHARMACOKINETICS OF GLYBURIDE IN NON-INSULIN DEPENDENT DIABETIC PATIENTS." DOCUMENTATION FOR THE INVESTIGATORS, ROBERT BLUM AND TADEUSZ KOTAS, TO CONDUCT PN-014 AT MILLARD FILLMORE HOSPITAL IN BUFFALO, NEW YORK IS ALSO ENCLOSED.
MEMO	AVANDIA	IND-43468	02/07/1995		AGREEMENT ON DOSES TO BE USED IN CARCINOGENICITY PROTOCOLS // 2/7/95 PHONE CONVERSATION IN WHICH HERMAN RHEE SAID THAT SB HAD ANSWERED ALL OF HIS QUESTIONS AND THE PROPOSED DOSES ARE ACCEPTABLE TO THE FDA, BUT A FORMAL APPROVAL LETTER WILL NOT BE ISSUED.
SUB	AVANDIA	IND-43468-S-023	02/24/1995		SUBMITTED THE CURRICULA VITAE OF DR. ROBERT PALMER AND DR. ALICE FLAGG, WHO ARE NOW RESPONSIBLE FOR THE REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF BRL-49653C.
SUB	AVANDIA	IND-43468-S-024	03/01/1995		SUBMITTED DOCUMENTATION FOR TEN NEW INVESTIGATORS: ALBERY, BLOCK, DECHERNEY, FIDDES, LITTLEJOHN, LUCAS, PEIRIS, ROSENBLATT, SCHWARTZ AND SERFER, TO CONDUCT STUDIES UNDER PN-006.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-025	03/03/1995		SUBMITTED AN INFORMATION AMENDMENT CONTAINING RESULTS FROM ONE CLINICAL PHARMACOKINETIC STUDY, HP-1001-BRL-049653-1, AND SEVENTEEN PRECLINICAL PHARMACOKINETIC / TOXICOLOGY STDUIES: TF-1034-BRL-049653-1, TF-1036-BRL-049653-1, TF-1020-BRL-049653-1, BF-1018-BRL-049653-1, BF-1012-BRL-049653-3, BF-1016-BRL-049653-1, BF-1022-BRL-049653-1, BF-1027-BRL-049653-1, BF-1013-BRL-049653-1, BF-1019-BRL-049653-1, BF-1020-BRL-049653-1, BF-1021-BRL-049653-1, BF-1014-BRL-049653-1, BF-1017-BRL-049653-1, BF-1010-BRL-049653-1, BF-1011-BRL-049653-1, AND BF-1015-BRL-049653-1.
SUB	AVANDIA	IND-43468-S-026	03/30/1995		SUBMITTED DOCUMENTATION FOR SIX ADDITIONAL NEW INVESTIGATORS: BRAUNSTEIN, CANNON, KIRKEGAARD, MCALLISTER, RENDELL AND PEIRIS, TO CONDUCT STUDY PN-BRL-49653C-006. REVISED DOCUMENTATION FOR ONE PREVIOUSLY SUBMITTED INVESTIGATOR, ROSENSTOCK, IS ALSO ENCLOSED.
SUB	AVANDIA	IND-43468-S-027	04/21/1995		SUBMITTED THE RESULTS OF FIVE PRECLINICAL TOXICOLOGY AND PHARMACOLOGY STUDIES: TF-1021-BRL-049653-2, BF-1026-BRL-049653-1, TF-1039-BRL-049653-1, TF-1035-BRL-049653-1 AND BF-1025-BRL-049653-1. ALSO SUBMITTED DATA FROM TWO REVISED STUDIES: TF-1011-BRL-049653-2 AND TF-1012-BRL-049653-2.
SUB	AVANDIA	IND-43468-S-028	04/28/1995		SUBMITTED DOCUMENTATION FOR FIVE NEW INVESTIGATORS, ANDERSON, GOLDSTEIN, HINSHAW, KIRBY AND WEINBERG, TO CONDUCT STUDIES UNDER PN-BRL-49653C-006.
SUB	AVANDIA	IND-43468-S-029	06/09/1995		SUBMITTED TWO FINAL CLINICAL REPORTS, HP-1003-BRL-049653-1 AND HP-1002-BRL-049653-1, CONTAINING THE RESULTS FROM TWO PHASE-1 CLINICAL STUDIES CONDUCTED WITH BRL-49653C.
SUB	AVANDIA	IND-43468-S-030	06/12/1995		INITIAL SAFETY REPORT OCCURRED IN IND-STUDY PN-006 (UNITED STATES), AE-95004941-1.
SUB	AVANDIA	IND-43468-S-031	06/20/1995		SUBMITTED DOCUMENTATION FOR THREE NEW INVESTIGATORS, DANDONA, LACKNER AND REAVEN, TO CONDUCT STUDIES UNDER PN-006. ALSO SUBMITTED REVISED INVESTIGATOR DOCUMENTATION FOR THREE SITES UNDER PN-006.
MEMO	AVANDIA	General	07/19/1995		ADVISORY COMMITTEE REVIEW OF PRECOSE (ACARBOSE) IN TYPE II DIABETES // DOCUMENTS THE 6/1/95 ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEETING REGARDING BAYER PHARMACEUTICALS PRECOSE (ACARBOSE), A NOVEL ANTI-DIABETIC COMPOUND WHICH ACTS LOCALLY IN THE G.I. TRACT TO BLUNT POSTPRANDIAL ABORPTION OF CARBOHYDRATES.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-032	08/01/1995		SUBMITTED MATERIALS PREVIOUSLY FAXED TO DR. RHEE AND FOUR FINAL STUDY REPORTS, TF-1037-BRL-049653-1, TF-1044-BRL-049653-1, TF-1043-BRL-049653-1 AND TF-1038-BRL-049653-1, FOR FOUR PRECLINICAL TOXICOLOGY STUDIES CONDUCTED IN SUPPORT OF THE RAT CARCINOGENICITY STUDIES.
SUB	AVANDIA	IND-43468-S-033	08/18/1995		SUBMITTED DOCUMENTATION FOR ONE ADDITIONAL INVESTIGATOR, W. MICHAEL RYAN, TO CONDUCT STUDIES UNDER PN-058.
SUB	AVANDIA	IND-43468-S-034	11/02/1995		SUBMITTED AN INITIAL SAFETY REPORT OF AN ADVERSE EVENT WHICH OCCURRED IN IND-STUDY PN-006 (UNITED STATES), AE-95011183-1 AND AE-95004941-1. ALSO SUBMITTED IS A COPY OF THE LETTER NOTIFYING THE INVESTIGATORS.
SUB	AVANDIA	IND-43468-S-036	11/29/1995		SUBMITTED A FOLLOW-UP SAFETY REPORT OF AN ADVERSE EVENT WHICH OCCURRED IN IND-STUDY PN-006 (UNITED STATES), AE-95004941-1.
SUB	AVANDIA	IND-43468-S-037	11/30/1995		SUBMITTED A NEW PROTOCOL, PN-030, ENTITLED, "A BIOEQUIVALENCE STUDY OF BRL-49653C PROPOSED FINAL MARKET TABLET FORMULATION (FORMULA AG-AA) VERSUS BRL-49653C CLINICAL TRIALS CAPSULE FORMULATION (FORMULA AB-AA)." DOCUMENTATION IS ENCLOSED FOR THE PRINCIPAL INVESTIGATOR, MARTIN FREED, TO CONDUCT STUDY PN-030. ITEM 7 CONTAINS CMC INFORMATION FOR A TABLET FORMULATION OF BRL-49653-C, EQUIVALENT TO 2.0 MG BRL-49653 PURE FREE BASE PER TABLET.
SUB	AVANDIA	IND-43468-S-038	12/14/1995		SUBMITTED A FOLLOW-UP SAFETY REPORT OF AN ADVERSE EVENT WHICH OCCURRED IN IND-STUDY PN-006 (UNITED STATES), AE-95011183-1. // INITIALLY SUBMITTED ON 11/2/95.
SUB	AVANDIA	IND-43468-S-039	12/22/1995		SUBMITTED AN ANNUAL REPORT FROM 9/23/94 THROUGH 9/22/95 INCLUDING INDIVIDUAL STUDY INFORMATION; SUMMARY INFORMATION; GENERAL INVESTIGATIONAL PLAN; INVESTIGATOR BROCHURE; AND FOREIGN MARKETING DEVELOPMENTS.
SUB	AVANDIA	IND-43468-S-035	01/15/1996		SUBMITTED AN INFORMATION AMENDMENT CONTAINING SIX PRECLINICAL STUDY REPORTS, TF-1040-BRL-049653-1, TF-1041-BRL-049653-1, TF-1042-BRL-049653-1, BF-1029-BRL-049653-1, BF-1030-BRL-049653-1 AND BF-1028-BRL-049653-1.
SUB	AVANDIA	IND-43468-S-040	01/23/1996		SUBMITTED THE FINAL STUDY REPORT FOR PN-002, SB REPORT NUMBER HP-1004-BRL-049653-1. STUDY REPORTS OF TWO PHASE-1 STUDIES, HJ-1001-BRL-049653-1-CPMS-017 AND HJ-1002-BRL-049653-1-CPMS-018, CONDUCTED IN JAPAN ARE ALSO ENCLOSED.

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SUB	AVANDIA	IND-43468-S-041	01/26/1996		SUBMITTED A NEW PROTOCOL, PN-029, ENTITLED, "EVALUATION OF THE SAFETY, TOLERABILITY AND PRELIMINARY PHARMACOKINETICS OF SINGLE RISING INTRAVENOUS DOSES OF BRL-49653C IN NORMAL VOLUNTEERS." DOCUMENTATION IS PROVIDED FOR THE PRINCIPAL INVESTIGATOR, MARTIN FREED, TO CONDUCT STUDY PN-029. ITEM 7 CONTAINS CMC INFORMATION FOR A 0.1 MG / ML AMPOULE FORMULATION OF BRL-49653C PURE FREE BASE (FORMULA AE).
SUB	AVANDIA	IND-43468-S-042	03/04/1996		SB REQUESTED AGENCY COMMENT FROM THE DIVISION AS TO WHETHER THE THREE STUDIES, PN-011, PN-015 AND PN-044, WOULD SUPPORT AN INDICATION FOR BOTH FIRST LINE (SINGLE AGENT) AND SECOND LINE (ADDED TO SULFONYLUREA OR METFORMIN THERAPY) TREATMENT IN NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM).
SUB	AVANDIA	IND-43468-S-043	03/12/1996		SUBMITTED A NEW PROTOCOL, PN-036, ENTITLED, "A STUDY TO DETERMINE THE EFFECT OF BRL-49653C ON THE PHARMACOKINETICS OF METFORMIN IN HEALTHY MALE VOLUNTEERS." DOCUMENTATION IS PROVIDED FOR THE PRINCIPAL INVESTIGATOR, HUNT, TO CONDUCT A STUDY UNDER PN-036.
SUB	AVANDIA	IND-43468-S-044	03/15/1996		SUBMITTED AN INFORMATION AMENDMENT CONTAINING FIFTEEN PRECLINICAL STUDY REPORTS, TF-1047-BRL-049653-1, PF-1007-BRL-049653-1, TF-1027-BRL-049653-1, TF-1032-BRL-049653-1, TF-1033-BRL-049653-1, TF-1031-BRL-049653-1, TF-1030-BRL-049653-1, TF-1024-BRL-049653-1, TF-1025-BRL-049653-1, PF-1005-BRL-049653-1, PF-1006-BRL-049653-1, PF-1008-BRL-049653-1, TF-1028-BRL-049653-1, TF-1029-BRL-049653-1 AND BF-1031-BRL-049653-1.
SUB	AVANDIA	IND-43468-S-045	04/26/1996		SUBMITTED A NEW PROTOCOL, PN-064, ENTITLED, "A BIOEQUIVALENCE STUDY OF METFORMIN COMMERCIAL TABLET FORMULATION (GLUCOPHAGE) VIRUS METFORMIN CLINICAL TRIALS CAPSULE FORMULATION." DOCUMENTATION IS PROVIDED FOR THE PRINCIPAL INVESTIGATOR, MARTIN FREED, TO CONDUCT STUDIES UNDER PN-064.
SUB	AVANDIA	IND-43468-S-046	04/30/1996		SUBMITTED A SUMMARY OF THE 3/22/96 TELECONFERENCE BETWEEN SB AND DR. GUERIGUIAN REGARDING THE ADEQUACY OF THREE PLANNED PIVOTAL PHASE-3 EFFICACY TRIALS TO SUPPORT THE USE OF BRL-49653C BOTH AS A SINGLE-AGENT FIRST-LINE THERAPY IN NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM), AND AS SECOND LINE, ADJUNCTIVE THERAPY, IN NIDDM PATIENTS WHO ARE NOT ADEQUATELY CONTROLLED ON A SULFONYLUREA OR METFORMIN.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-047	05/29/1996		SUBMITTED A REQUEST FOR AN END OF PHASE-2 MEETING TO SEEK THE AGENCY"S ADVICE AND REACH AN AGREEMENT ON THE KEY FEATURES OF THE PROPOSED PHASE-3 CLINICAL PROGRAM. ALSO SUBMITTED A PROPOSED AGENDA, A TENTATIVE LIST OF SB PARTICIPANTS, AND A REQUEST THAT APPROPRIATE EXPERTS FROM THE FDA PARTICIPATE.
SUB	AVANDIA	IND-43468-S-048	05/30/1996		SUBMITTED TWO FINAL CLINICAL STUDY REPORTS, HP-1005-BRL-049653-1 FOR PN-014 AND HP-1006-BRL-049653-1 FOR PN-016.
MEMO	AVANDIA	General	06/10/1996		END OF PHASE 2 MEETING DATE // 6/7/96 CONVERSATION IN WHICH ENID GALLIERS SAID THAT 7/22/96 WAS THE EARLIEST DATE WHICH THOSE IN THE DIVISION, REQUIRED FOR THE END OF PHASE-2 MEETING, WOULD BE AVAILABLE TO MEET WITH SB.
SUB	AVANDIA	IND-43468-S-049	06/14/1996		SUBMITTED A NEW PROTOCOL, PN-037, ENTITLED, "A STUDY TO ASSESS THE EFFECT OF RANITIDINE ON THE BIOAVAILABILITY OF BRL-49653C IN HEALTHY ADULT MALES." ALSO SUBMITTED DOCUMENTATION FOR THE PRINCIPAL INVESTIGATOR, MARTIN FREED, TO CONDUCT STUDIES UNDER PN-037. ITEM 7 CONTAINS CMC INFORMATION FOR 1.0, 2.0 AND 4.0 MG TABLET FORMULATIONS, FORMULAS AN, AG AND BD, RESPECTIVELY, AND MATCHING PLACEBO, FORMULA EF.
SUB	AVANDIA	IND-43468-S-050	06/28/1996		SUBMITTED A BRIEFING DOCUMENT FOR THE 7/22/96 END OF PHASE-2 MEETING TO DISCUSS PHASE-3 CLINICAL DEVELOPMENT.
CFF	AVANDIA	IND-43468	06/28/1996		(FAX) FDA PROVIDED THE SCHEDULE AND LIST OF FDA ATTENDEES FOR THE 7/22/96 END OF PHASE-2 MEETING.
SUB	AVANDIA	IND-43468-S-051	07/10/1996		SUBMITTED A NEW PROTOCOL, PN-034, ENTITLED, "A STUDY TO ASSESS THE EFFECT OF BRL-49653C ON THE PHARMACOKINETICS OF DIGOXIN IN HEALTHY ADULT MALES." ALSO SUBMITTED DOCUMENTATION FOR THE PRINCIPAL INVESTIGATOR, MARTIN FREED.
SUB	AVANDIA	IND-43468-S-052	07/17/1996		SUBMITTED A NEW PHASE-3 PROTOCOL, PN-BRL-49653-011, ENTITLED, "A 26 WEEK RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED, COMPARISON STUDY TO EVALUATE THE SAFETY, EFFICACY, AND TOLERABILITY OF BRL-49653C THERAPY WHEN ADMINISTERED TO PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM)." ALSO SUBMITTED DOCUMENTATION FOR THE FIRST INVESTIGATOR, CHARLES HUH, TO CONDUCT A STUDY UNDER PN-011.

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SUB	AVANDIA	IND-43468-S-053	07/31/1996		SUBMITTED MINOR MODIFICATIONS TO THE ROUTE B SYNTHESIS OF DRUG SUBSTANCE PREVIOUSLY SUBMITTED ON 1/30/95. A REVISED METHOD OF MANUFACTURE, REVISED DRUG SUBSTANCE SPECIFICATION AND BATCH DATA ARE PROVIDED. THE SPECIFICATION HAS BEEN REVISED TO REMOVE A NAMED IMPURITY, SB-214520, WHICH WAS RELEVANT TO ROUTE A BUT IS NOT APPLICABLE TO ROUTE B MANUFACTURE. ALSO UPDATED STABILITY DATA ARE PROVIDED FOR ROUTE A AND ROUTE B MANUFACTURE.
SUB	AVANDIA	IND-43468-S-054	08/16/1996		SUBMITTED DOCUMENTATION FOR EIGHTEEN NEW INVESTIGATORS, SANDALL, LITTLEJOHN, LEWIN, DRUCKER, ROSENBLATT, WILLIAMS, MORIN, GILDERMAN, MARBURY, WEISS, CHATTMAN, SCHWARTZ, ALWINE, HSI, KOFF, FIDDES, BLOCK AND HEATLEY, TO CONDUCT STUDIES UNDER PN-011.
SUB	AVANDIA	IND-43468-S-055	08/29/1996		SUBMITTED SB"S MEETING MINUTES FROM THE 7/22/96 END OF PHASE 2 MEETING WITH THE FDA DURING WHICH PHASE 3 CLINICAL DEVELOPMENT OF BRL-49653C WAS DISCUSSED.
SUB	AVANDIA	IND-43468-S-056	09/16/1996		SUBMITTED DOCUMENTATION FOR TWENTY ADDITIONAL INVESTIGATORS, PODLECKI, GOLDSTEIN, MCALLISTER, CAPUZZI, BALLONOFF, ROSENSTOCK, GORE, PEK, MARCUS, DECHERNEY, BERGER, HINSHAW, PATRON, PEIRIS, LICATA, RENDELL, KIRKEGAARD, DANDONA, DEABATE AND ANDERSON, TO CONDUCT STUDIES UNDER PN-011.
SUB	AVANDIA	IND-43468-S-057	09/24/1996		SUBMITTED A PHASE-3 PROTOCOL, PN-080, ENTITLED, "A 52 WEEK OPEN LABEL, MULTICENTER, ACTIVE (GLYBURIDE) COMPARISION STUDY, TO EVALUATE THE EFFECT OF BRL-49653C ON CARDIOVASCULAR FUNCTION IN PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM)." ALSO SUBMITTED DOCUMENTATION FOR THE FIRST INVESTIGATOR, DEEPAK SANT RAM, TO CONDUCT PN-080. // LEFT VENTRICULAR MASS INDEX; LVMI; M MODE ECHOCARDIOGRAPHY
SUB	AVANDIA	IND-43468-S-058	10/24/1996		SUBMITTED A NEW PROTOCOL, PN-035, ENTITLED, "A STUDY TO ASSESS THE EFFECT OF BRL-49653C ON THE ANTICOAGULANT EFFECT OF WARFARIN IN HEALTHY MALE VOLUNTEERS." ALSO, SUBMITTED DOCUMENTATION FOR THE PRINCIPAL INVESTIGATOR, KAZIERAD, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-035. // PHASE-3

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SUB	AVANDIA	IND-43468-S-059	10/30/1996		SUBMITTED DOCUMENTATION FOR FIVE NEW INVESTIGATORS, BURKE, LEBOVITZ, CHAIKEN, BOWEN AND JOHNSON, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-011. ALSO, SUBMITTED DOCUMENTATION FOR NEW INVESTIGATORS, BIDOT, LARACH, CONWAY, RENDELL, LITTLEJOHN, ROSENSTOCK, FRANCO, FIDDES, SCHWARTZ, ALBERY, WEISS, JAIN, TANDRON, IVERSON, ROSENBLATT, AND WEINBERG, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-080. // PHASE-3
SUB	AVANDIA	IND-43468-S-060	11/08/1996		SUBMITTED A RESPONSE TO THE PHARMACOLOGY REVIEWER"S 9/20/96 QUESTIONS REGARDING THE PRECLINICAL ASPECTS OF SB"S 8/29/96 SUBMISSION. PROVIDED FROM THE 6/28/96 END OF PHASE-2 MEETING BRIEFING DOCUMENT PHARMACOKINETIC, TOXICOKINETIC, AND METABOLIC DATA FOR SPECIES USED FOR TOXICOLOGY STUDIES. ALSO PROVIDED INFORMATION ON THE EXPOSURE RATIO (AUC) OF THE ANIMALS TO HUMAN FOR THE LOWEST DOSES AT WHICH CARDIAC HYPERTROPHY, HYDROTHORAX AND/OR ANEMIA OCCURRED AND OUTLINED THE EFFORT CURRENTLY DIRECTED TO SEARCH FOR THE UNDERSTANDING OF THE MECHANISTIC ACTION OF THIS DRUG. // PEROXISOMAL PROLIFERATOR ACTIVATED RECEPTOR GAMMA; INSULIN SENSITIVITY; PHASE-3; METABOLIC PROFILE; ANTIDIABETIC EFFECT; DECREASED HEMATOCRIT; VASCULAR EFFECTS
SUB	AVANDIA	IND-43468-S-062	11/27/1996		SUBMITTED DOCUMENTATION FOR ONE NEW INVESTIGATOR, PORTE, TO CONDUCT A STUDY UNDER PN-011; AND TWO NEW INVESTIGATORS, DANDONA AND LUCAS, TO CONDUCT STUDIES UNDER PN-080.
SUB	AVANDIA	IND-43468-S-061	12/03/1996		SUBMITTED A NEW PHASE-3 PROTOCOL, PN-49653-024, ENTITLED, "A 26 WEEK RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED, STUDY TO EVALUATE THE SAFETY, EFFICACY, AND TOLERABILITY OF BRL-49653C THERAPY WHEN ADMINISTERED TO PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM) USING ONCE DAILY DOSING REGIMEN, AND TO DETERMINE THE THERAPEUTIC EQUIVALENCE OF THE ONCE AND TWICE DAILY DOSING REGIMENS." ALSO SUBMITTED DOCUMENTATION FOR THE FIRST INVESTIGATOR, TRUJILLO, TO CONDUCT A STUDY UNDER PN-024. ITEM 7 CONTAINS CMC INFORMATION FOR THE 1.0, 2.0 AND 4.0 MG TABLET FORMULATIONS.
MEMO	AVANDIA	GENERAL	12/11/1996		DOCUMENTS MEETING MINUTES OF THE ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE ON REZULIN AND PRELAY.

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SUB	AVANDIA	IND-43468-S-063	12/20/1996		SUBMITTED AN ANNUAL REPORT FOR THE PERIOD FROM 9/23/95 THROUGH 9/22/96 INCLUDING INDIVIDUAL STUDY INFORMATION, SUMMARY INFORMATION AND GENERAL INVESTIGATIONAL PLAN. // PHASE-3
SUB	AVANDIA	IND-43468-S-064	12/31/1996		SUBMITTED DOCUMENTATION FOR 44 NEW INVESTIGATORS, PATRON, MORIN, MOHAN, MILLER, HUH, WEISS, MCALLISTER, NORTON, TOTH, NOVECK, FIDDES, RESNICK, BRUNE, FREEMAN, DECHERNEY, RICHARD, REYNOLDS, KLAFF, BURGE, TUCKER, GABRIEL, ROSENBLATT, PITA, WEINSTEIN, HIPPERT, MOORE, MULLICAN, BAGDADE, BASKETT, DELCHER, GREMILLION, HENRY, HSI, LEWIN, MAGGIACOMO, MATLOCK, BARRERA, WYSHAM, EARL, REDMOND, STOKES, BOWLING, GOVE AND PASTER, WHO WILL CONDUCT STUDIES UNDER PN-024. // PHASE-3
SUB	AVANDIA	General	01/07/1997		(FAX) SUBMITTED INVESTIGATOR DOCUMENTATION FOR ROBERT A. FIDDES WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-006.
SUB	AVANDIA	IND-43468-S-065	01/09/1997		SUBMITTED AN INITIAL SAFETY REPORT, AE-96018299-1, OF AN ADVERSE EVENT WHICH OCCURRED IN NON-IND-STUDY PN-015 (UNITED KINGDOM). // MYOCARDIAL INFARCTION
CFF	AVANDIA	IND-43468	01/15/1997		(FAX) FDA PROVIDED COMMENTS AND QUESTIONS REGARDING PRECLINICAL PHARMACOLOGY DATA REFERENCED IN THE 3/29/96 ANNUAL REPORT. // EXPOSURE RATIO FOR HIGH DOSE SELECTION; HEART WEIGHT INCREASES; PERIPHERAL VASODILATION; AUTONOMIC NERVOUS SYSTEM; BRL 49653C-INDUCED CLINICAL SYMPTOMS; AUC RATIOS; RODENT CARCINOGENICITY STUDY; DRY MOUTH; GASTROESOPHAGEAL REFLEX; MYALAGIA // PER 1/15/97 MEMO FDA IS REFERRING TO SEVERAL PRECLINICAL REPORTS SUBMITTED ON 3/15/96 AND REFERENCED IN THE 3/29/96 ANNUAL REPORT
MEMO	AVANDIA	IND-43468	01/15/1997		BRL-49653 FDA PHARMACOLOGY / TOXICOLOGY COMMENTS // DOCUMENTS THE RECEIPT OF A 1/15/97 FAX FROM THE FDA IN WHICH DR. RHEE, THE PRECLINICAL REVIEWER FOR BRL-49653, LISTED SEVERAL COMMENTS FROM THE PHARMACOLOGY REVIEW OF THE 3/26/96 ANNUAL REPORT. // NO SUBMISSION OF 3/26/96, BUT REFERS TO 3/15/96 SUBMISSION
SUB	AVANDIA	IND-43468-S-066	01/16/1997		SUBMITTED DOCUMENTATION FOR 15 NEW INVESTIGATORS, MITCHELL, GRUNBERGER, SKOBELOFF, COLLINS, FARMER, HERBST, ROSENBLOOM, RENJIFRO, ROUDEBUSH, NADEAU, HOLMES, MILLER, ZIGRANG, TEUTSCH AND DANDONA, TO CONDUCT STUDIES UNDER PN-024. // NON-INSULIN DEPENDENT DIABETES MELLITUS; PHASE-3

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SUB	AVANDIA	IND-43468-S-067	01/22/1997		SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-96018299-1. // NON-IND-STUDY PN-015 (UNITED KINGDOM)
SUB	AVANDIA	IND-43468-S-068	01/27/1997		SUBMITTED TO PROTOCOL PN-035 AMENDMENT 2 WHICH ALLOWS FOR THE ADDITIONAL STUDY OF FOUR SUBJECTS WHO HAD INCREASES IN INTERNATIONAL NORMALIZED RATIO OF WARFARIN DOSE (INR) OF 25 PERCENT OR MORE DURING THE DOUBLE BLIND TREATMENT PHASE COMPARED TO BASELINE INR (THE MEAN INR ON DAYS 12-14 INCLUSIVE). // PHASE-1; ANTICOAGULANT
SUB	AVANDIA	IND-43468-S-069	01/31/1997		SUBMITTED TWO FINAL STUDY REPORTS BRL-049653-RSD-1005TC-1 FOR PN-029 AND BRL-049653-RSD-1006FL-1 FOR PN-036. // PHARMACOKINETICS; METFORMIN; PHASE-3
SUB	AVANDIA	IND-43468-S-070	02/21/1997		SUBMITTED DOCUMENTATION FOR THREE NEW INVESTIGATORS, SCHARYJ, PHILLIPS AND SMITH, TO CONDUCT STUDIES UNDER PN-024 AND THREE NEW INVESTIGATORS, DAVIDSON, BERGER, AND HUH, TO CONDUCT STUDIES UNDER PN-080. // PHASE-3; NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM)
SUB	AVANDIA	IND-43468-S-073	02/25/1997		SUBMITTED A PHASE-3 PROTOCOL, PN-096, ENTITLED, "A 26-WEEK RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF BRL-49653C WHEN ADMINISTERED ONCE DAILY TO PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM) WHO ARE INADEQUATELY CONTROLLED ON AT LEAST HALF-MAXIMAL DOSE (GREATER THAN OR EQUAL TO 10 MG/DAY) OF GLYBURIDE." ALSO, DOCUMENTATION IS PROVIDED FOR THE FIRST INVESTIGATOR, ZORBA PASTER, TO CONDUCT A STUDY UNDER PN-096. // PHASE-3; HYPERGLYCEMIA
SUB	AVANDIA	IND-43468-S-071	02/25/1997		SUBMITTED A PHASE-3 PROTOCOL, PN-079, ENTITLED, "A 26-WEEK RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, MULTICENTERED, STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF BRL-49653C WHEN ADMINISTERED TO PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM) WHO ARE INADEQUATELY CONTROLLED ON A MAXIMAL DOSE (20 MG/DAY) OF GLYBURIDE." ALSO, SUBMITTED UPDATED CMC INFORMATION FOR THE 1 MG, 2 MG AND 4 MG FORMULATIONS, AN OVERENCAPSULATED 10 MG GLYBURIDE PRODUCT (FORMULA CODE AA) AND A PLACEBO CAPSULE (FORMULA CODE JN). LABELS FOR THE CLINICAL STUDY ARE ALSO INCLUDED. // PHASE-3

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-074	02/26/1997		SUBMITTED A PHASE-3 PROTOCOL, PN-094, ENTITLED, "A 26-WEEK RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF BRL-49653C WHEN ADMINISTERED ONCE DAILY TO PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM) WHO ARE INADEQUATELY CONTROLLED ON A MAINTENANCE DOSE (2.5 G/DAY) OF METFORMIN." ALSO, DOCUMENTATION IS PROVIDED FOR THE FIRST INVESTIGATOR, SHERWYN SCHWARTZ, TO CONDUCT A STUDY UNDER PN-094. // PHASE-3; HYPERGLYCEMIA
SUB	AVANDIA	IND-43468-S-075	02/28/1997		SUBMITTED, IN RESPONSE TO MIKE JOHNSTON"S 11/6/96 REQUEST, ECG DATA FOR POST-RANDOMIZATION VISITS IN STUDY PN-014. // HP-1006-BRL-049653-1; PHASE-3
SUB	AVANDIA	IND-43468-S-072	03/12/1997		SUBMITTED AN INITIAL SAFETY REPORT, AE-97002849-1, OF AN ADVERSE EVENT WHICH OCCURRED IN NON-IND-STUDY PN-015 (UNITED KINGDOM). ALSO SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-96018299-1, INITIALLY SUBMITTED ON 1/9/97. // PROBABLE MYOCARDIAL INFARCTION; PHASE-3
SUB	AVANDIA	IND-43468-S-076	03/13/1997		SUBMITTED A PHASE-1 PROTOCOL, PN-007, ENTITLED, "AN EVALUATION OF THE PHARMACOKINETICS OF A SINGLE ORAL DOSE OF BRL-49653C IN HEMODIALYSIS-DEPENDENT PATIENTS WITH END STAGE RENAL DISEASE COMPARED TO VOLUNTEERS WITH NORMAL RENAL FUNCTION." ALSO SUBMITTED DOCUMENTATION FOR MARTIN FREED TO CONDUCT A STUDY UNDER PN-007. // PHASE-1

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SUB	AVANDIA	IND-43468-S-078	03/26/1997		SUBMITTED DOCUMENTATION FOR NEW INVESTIGATOR, KITABCHI, TO CONDUCT A STUDY UNDER PN-024; 21 NEW INVESTIGATORS, STRAUSS, BOWLING, LEICHTER, SUWANNASRI, MILLER, MORIN, ALWINE, JAIN, LITTLEJOHN, BERGER, RUDOLPH, PONTE, KIPNESS, LAND, WEISS, COHEN, WEISMAN, PATRON, JOHNSTON, SANDALL AND SPISAK, TO CONDUCT STUDIES UNDER PN-096; 23 NEW INVESTIGATORS, WEISS, MERSEY, DICKE, KASSMAN, HIGGINS, HERRON, ROSENBLATT, LEFTON, LEWIN, GRAF, RENDELL, TOFFEL, CHAVEZ, HOLT, STRUTIN, BIDOT, GORDON, D"ANGELO, JOHNSON, GAMAN, PODLECKI, TOTH AND ARONOFF, TO CONDUCT STUDIES UNDER PN-079; AND 30 NEW INVESTIGATORS, NADEAU, WEERASINGHE, TOUGER, HUH, ROSENSTOCK, NEUTEL, HSI, DREHOBL, TANDRON, WAHLEN, POHL, RENDELL, RIPLEY, SHELANSKI, MILLER, ERVIN, TEUTSCH, GOLDSTEIN, FISHER, AZORR, SPERLING, CLINKINGBEARD, MCCARTNEY, WYSHAM, COLE, RIEDERMAN, HEATLEY, KERN, STERNER AND REDMOND, TO CONDUCT STUDIES UNDER PN-094. // PHASE-3
SUB	AVANDIA	IND-43468-S-077	03/26/1997		SUBMITTED TWO FINAL STUDY REPORTS, SB REPORT NUMBER BRL-049653-RSD-100DG9-1 FOR STUDY PN-037, AND SB REPORT NUMBER BRL-049653-RSD-1006FM-1 FOR STUDY PN-064. // PHASE-3; RANITIDINE; METFORMIN; GLUCOPHAGE
SUB	AVANDIA	IND-43468-S-079	04/04/1997		SUBMITTED RESPONSES TO DR. PHEE"S FAX OF 1/15/97 CONTAINING QUESTIONS ON PRECLINICAL ASPECTS OF BRL-49653C. // PHASE-3; EXPOSURE RATIO; AUC; SYMPATHETIC DRIVE; RENAL CATECHOLAMINE CONCENTRATIONS; RENAL SYMPATHETIC NERVE ACTIVITY; GASTROESOPHAGEAL REFLUX; MYALGIA
SUB	AVANDIA	IND-43468-S-080	04/11/1997		SUBMITTED A NEW PHASE-3 PROTOCOL, PN-093, ENTITLED, "A 26-WEEK RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, MULTICENTER STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF BRL-49653C 4 MG BID WHEN ADMINISTERED TO PATIENTS WITH NIDDM WHO ARE INADEQUATELY CONTROLLED ON A MAINTENANCE DOSE (2.5 G/ DAY) OF METFORMIN." // PHASE-3
SUB	AVANDIA	IND-43468-S-081	04/11/1997		SUBMITTED A PHASE-3 EXTENSION PROTOCOL, PN-084, ENTITLED, "AN OPEN-LABEL EXTENSION STUDY TO ASSESS LONG-TERM SAFETY, TOLERABILITY AND EFFICACY OF BRL-49653C WHEN ADMINISTERED AS MONOTHERAPY, TWICE DAILY, TO PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM)." // PHASE-3

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SUB	AVANDIA	IND-43468-S-082	04/18/1997		SUBMITTED A NEW PROTOCOL, PN-008, ENTITLED, "AN EVALUATION OF THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PROTEIN BINDING OF BRL-49653C IN PATIENTS WITH HEPATIC IMPAIRMENT." ALSO SUBMITTED DOCUMENTATION FOR THE FIRST INVESTIGATOR, SCHENKER, TO CONDUCT A STUDY UNDER PN-008. // PHASE-2
SUB	AVANDIA	IND-43468-S-083	04/23/1997		SUBMITTED A PHASE-3 PROTOCOL, PN-090, ENTITLED, "AN 8 WEEK RANDOMIZED, DOUBLE BLIND, MULTICENTER, PLACEBO CONTROLLED, PARALLEL GROUP, DOSE RANGING STUDY TO EVALUATE THE SAFETY, EFFICACY AND TOLERABILITY OF BRL-49653C THERAPY WHEN ADMINISTERED TO PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM) USING A TWICE DAILY DOSING REGIMEN." // PHASE-3
SUB	AVANDIA	IND-43468-S-084	04/29/1997		SUBMITTED DOCUMENTATION FOR SIX NEW INVESTIGATORS, ROTH, WOOL, GOLDSTEIN, LUCAS, DANDONA AND ENZMANN, TO CONDUCT STUDIES UNDER PN-079; 14 NEW INVESTIGATORS, GILDERMAN, MORIN, KOFF, PATRON, MARBURY, BLOCK, MCALLISTER, HEATLEY, ALWINE, DRUCKER, SANDALL, LEWIN, HSI AND WEISS, TO CONDUCT STUDIES UNDER PN-084; 14 NEW INVESTIGATORS, KLAFF, CAOS, LACKNER, MARBURY, EIL, RAJAN, SCULLY, LIPETZ, GILDERMAN, SANT RAM, MARKUNAS, MEZITIS, CONWAY AND TOTH, TO CONDUCT STUDIES UNDER PN-093; THREE NEW INVESTIGATORS, BURKE, THRONE AND TIDMAN, TO CONDUCT STUDIES UNDER PN-094; AND NINE NEW INVESTIGATORS, EISENBUD, ADAMS, MCGILL, STONE, MANGNIONE, RICHARDSON, ANDERSON, GOVE, AND FELICETTA, TO CONDUCT STUDIES UNDER PN-096. // PHASE-3
SUB	AVANDIA	IND-43468-S-086	05/09/1997		SUBMITTED A NEW PROTOCOL, PN-038, ENTITLED, "AN EVALUATION OF THE PHARMACOKINETICS OF A SINGLE ORAL DOSE OF BRL-49653C IN PATIENTS WITH VARYING DEGREES OF RENAL INSUFFICIENCY COMPARED TO VOLUNTEERS WITH NORMAL RENAL FUNCTION." ALSO SUBMITTED DOCUMENTATION FOR TWO NEW INVESTIGATORS, SACK AND SIMPSON, TO CONDUCT STUDIES UNDER PN-038. // PHASE-2
SUB	AVANDIA	IND-43468-S-085	05/09/1997		SUBMITTED 13 PRECLINICAL REPORTS: RSD-100BFZ-1, RSD-1009ZS-1, TF-1046, PF-1009, PF-1010, RSD-100BF5-1, RSD-100HRG-1, RSD-1005S3-1, TF-1045, RSD-1005C0-1, RSD-100J8G-1, RSD-100CPZ-1 AND RSD-100DJ2-1. // PHASE-3

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SUB	AVANDIA	IND-43468-S-087	05/21/1997		SUBMITTED DOCUMENTATION FOR ONE NEW INVESTIGATOR, STEVENS, TO CONDUCT A STUDY UNDER PN-024; FOUR NEW INVESTIGATORS, LEVIN, PORTE, GARBER AND GOLDBERG, TO CONDUCT STUDIES UNDER PN-079; ELEVEN NEW INVESTIGATORS, SCHWARTZ, ANDERSON, PODLECKI, HUH, DECHERNEY, ROSENBLATT, ROSENSTOCK, RENDELL, GORE, BERGER AND LICATA, TO CONDUCT STUDIES UNDER PN-084; TWENTY NEW INVESTIGATORS, BRODY, FARMER, SUGIMOTO, WILLIAMS, PAOLINO, HSI, WEINSTEIN, IVERSON, CATHCART, HERSHON, KOFF, WILSON, WINGERT, LEWIN, ROSENBLATT, HERBST, MERSEY, MURRAY, GABRIEL AND ISAACSOHN, TO CONDUCT STUDIES UNDER PN-090; TEN NEW INVESTIGATORS, FIORILLO, WILLIAMS, GILLIE, SHAPIRO, BUSICK, ISAACSOHN, PHILLIPSON, BROWN-REUSCH, THEEN AND SANTAN, TO CONDUCT STUDIES UNDER PN-093; TWO NEW INVESTIGATORS, FONSECA AND GREENBERG, TO CONDUCT STUDIES UNDER PN-094; AND TWO NEW INVESTIGATORS, HERRON AND PORTE, TO CONDUCT STUDIES UNDER PN-096. // PHASE-2; PHASE-3
SUB	AVANDIA	IND-43468-S-088	05/23/1997		SUBMITTED MODIFICATION TO PROTOCOLS PN-079, PN-096 AND PN-094. LISTINGS OF THE CHANGES FOR EACH PROTOCOL ARE PROVIDED ALONG WITH COPIES OF THE REVISED PROTOCOLS. // GLYBURIDE; ANTIDIABETIC THERAPY; HEMOGLOBINOPATHIES; INCLUSION CRITERIA; EXCLUSION CRITERIA; APPETITE SUPPRESSANTS; DEXFENFLURAMINE HYDROCHLORIDE; PHENTERMINE HYDROCHLORIDE; FENFLURAMINE HYDROCHLORIDE; BLOOD PRESSURE MEASUREMENTS; MERCURY COLUMN SPHYGMOMANOMETER; WITHDRAWAL PROCEDURE; BILIRUBIN; AST; ALT; ALKALINE PHOSPHATASE; METFORMIN; LACTIC ACID LEVELS; PLETHYSMOGRAPHIC METHOD; TREATMENT OF OVERDOSAGE; HYPOGLYCEMIA; BLOOD AND URINE SPECIMENS; HOMEOSTASIS MODEL ASSESSMENT; HOMA; INSULIN RESISTANCE; BETA CELL FUNCTION; INSULIN SENSITIVITY; PRIMARY EFFICACY PARAMETER; WITHDRAWAL CRITERIA; INFORMED CONSENT; PHASE-3
SUB	AVANDIA	IND-43468-S-089	06/04/1997		SUBMITTED TO PROTOCOL PN-008 AMENDMENT 1 WHICH DELETES THE REQUIREMENT THAT HEPATIC PATIENTS DEMONSTRATE AN ELEVATED PROTHROMBIN TIME GREATER THAN 1.2 TIMES THE UPPER LIMIT OF THE LABORATORY REFERENCE RANGE. // PROTEIN BINDING; INCLUSION CRITERIA; HEPATIC DISEASE SCORING SYSTEM

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SUB	AVANDIA	IND-43468-S-090	06/05/1997		SUBMITTED A NEW PROTOCOL, PN-082, ENTITLED, "A 26-WEEK RANDOMIZED, DOUBLE-BLIND, MULTICENTER STUDY TO EVALUATE THE SAFETY, EFFICACY, AND TOLERABILITY OF BRL 49653C WHEN ADMINISTERED TWICE DAILY TO PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM) WHO ARE INADEQUATELY CONTROLLED ON INSULIN MONOTHERAPY." // PHASE-3; COMBINATION THERAPY; REDUCTION OF HYPERGLYCEMIA; 2 MG BID; 4 MG BID; FASTIN PLASMA GLUCOSE; 140 MG/DL; HBA1C
SUB	AVANDIA	IND-43468-S-091	06/10/1997		SUBMITTED A NEW PROTOCOL, PN-040, ENTITLED, "EFFECT OF ACARBOSE ON THE PHARMACOKINETICS OF BRL 49653C IN HEALTHY ADULT VOLUNTEERS." ALSO SUBMITTED DOCUMENTATION FOR THE FIRST INVESTIGATOR, MARTIN FREED. // PHASE-2; STANDARDIZED MEAL; SAFETY AND TOLERABILITY OF A SINGLE ORAL DOSE; TWO PERIOD, OPEN LABEL STUDY
SUB	AVANDIA	IND-43468-S-092	06/10/1997		SUBMITTED A NEW PHASE-3 PROTOCOL, PN-095, ENTITLED, "A 26-WEEK RANDOMIZED, DOUBLE-BLIND, MULTICENTER STUDY TO EVALUATE THE SAFETY, EFFICACY, AND TOLERABILITY OF BRL 49653C WHEN ADMINISTERED ONCE DAILY TO PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM) WHO ARE INADEQUATELY CONTROLLED ON INSULIN MONOTHERAPY." // PHASE-2; COMBINATION THERAPY; HYPERGLYCEMIA
SUB	AVANDIA	IND-43468-S-093	06/18/1997		SUBMITTED DOCUMENTATION FOR ONE NEW INVESTIGATOR, BLUM, TO CONDUCT A STUDY UNDER PN-038; TWO NEW INVESTIGATORS, GRUNBERGER AND DAVIS, TO CONDUCT STUDIES UNDER PN-079; ONE NEW INVESTIGATOR, HENRY, TO CONDUCT A STUDY UNDER PN-080; EIGHT NEW INVESTIGATORS, MEZITIS, SMITH, BOWLING, LEWIN, GRINGERI, ROSENSTOCK, STOKES AND SCHWARTZ, TO CONDUCT STUDIES UNDER PN-082; FOURTEEN NEW INVESTIGATORS, BURKE, DANDONA, HINSHAW, BALLONOFF, MULLICAN, PATEL, CHAMPION, REUSCH, LICATA, REDMOND, HENRY, AMIN, MULMED AND RASKIN, TO CONDUCT STUDIES UNDER PN-090; SEVEN NEW INVESTIGATORS, REASNER, DOYLE, SNYDER, ROMAN, CRANDALL, WITTLIN AND RASKIN, TO CONDUCT STUDIES UNDER PN-093; ONE NEW INVESTIGATOR, HSUEH, TO CONDUCT A STUDY UNDER PN-094; AND THREE NEW INVESTIGATORS, GUERIN, MARBURY AND RENDELL, TO CONDUCT STUDIES UNDER PN-095. // PHASE-2; PHASE-3

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SUB	AVANDIA	IND-43468-S-094	06/20/1997		SUBMITTED A NEW PROTOCOL, PN-097, ENTITLED "A 52-WEEK OPEN LABEL, MULTICENTER, ACTIVE GLYBURIDE COMPARISON STUDY, TO EVALUATE THE EFFECT OF BRL 49653C 8 MG UID ON CARDIOVASCULAR FUNCTION IN PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM)." // LEFT VENTRICULAR MASS INDEX (LVMI); PHASE-3
SUB	AVANDIA	IND-43468-S-095	06/24/1997		SUBMITTED AN INITIAL SAFETY REPORT, AE-97014135-1, OF AN ADVERSE EVENT WHICH OCCURRED IN IND-STUDY PN-024 (UNITED STATES). ALSO SUBMITTED A COPY OF THE LETTER, WHICH WAS SENT TO ALL UNITED STATES INVESTIGATORS CONDUCTING CLINICAL TRIALS WITH BRL-49653, UPDATING THE INVESTIGATOR BROCHURE TO INCLUDE THE ADVERSE EXPERIENCE, ANEMIA. // PHASE-3; DEAR DOCTOR LETTER
MEMO	AVANDIA	GENERAL	06/24/1997		SUBMITTED INITIALED STATEMENT OF ADOPTION. NOTED THAT THE SECOND CHEMICAL NAME HAS A TYPOGRAPHICAL ERROR.
SUB	AVANDIA	IND-43468-S-096	07/10/1997		SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-97014135-1, INITIALLY SUBMITTED ON 6/24/97. // IND-STUDY PN-024 (UNITED STATES)
SUB	AVANDIA	IND-43468-S-098	07/15/1997		SUBMITTED DOCUMENTATION FOR ONE NEW INVESTIGATOR, BLUM, TO CONDUCT A STUDY UNDER PN-008; THREE NEW INVESTIGATORS, DREBOHL, REDMOND AND SNYDER, TO CONDUCT STUDIES UNDER PN-079; TWENTY-TWO NEW INVESTIGATORS, BLOCK, BURNETT, CLINKINGBEARD, COLLINS, EVANS, GONZALEZ, HIGGINS, JAIN, KILO, KLAFF, LACAVA, MORIN, PODLECKI, RENDELL, REYNERTSON, RIDDLE, ROSANSKY, STONE, TOTH, WYSHAM, AHMANN AND BARRERA, TO CONDUCT STUDIES UNDER PN-082; FOUR NEW INVESTIGATORS, CATHCART, LEBOVITZ, CHAIKEN AND PEK, TO CONDUCT STUDIES UNDER PN-084; FOUR NEW INVESTIGATORS, BLONDE, KILO, ORLANDER AND STUART, TO CONDUCT STUDIES UNDER PN-090; THREE NEW INVESTIGATORS, BELL, MILAN AND SCHWARTZ, TO CONDUCT STUDIES UNDER PN-093; THIRTEEN NEW INVESTIGATORS, ARONOFF, COLE, CONWAY, DECHERNEY, DELCHER, ENZMANN, FARMER, GORE, GRAF, MILLER, PATRON, ROSENBLOOM AND SORENSON, TO CONDUCT STUDIES UNDER PN-095; AND SIXTEEN NEW INVESTIGATORS, ALBERY, COLE, CONWAY, HENRY, HERSHON, LA CAVA, LITTLEJOHN. NEUTEL, REDMOND, ROSENBLATT, ROSENBLOOM, ROSENSTOCK, RUBINO, TOTH, WEERASINGHE AND WEISS, TO CONDUCT STUDIES UNDER PN-097. // PHASE3
SUB	AVANDIA	IND-43468-S-097	07/15/1997		SUBMITTED A COPY OF THE MOST RECENT EDITION OF THE INVESTIGATIR BROCHURE, DATED 2//97, WHICH REPLACES THE PREVIOUS EDITION OF 6//95. // PHASE-3

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SUB	AVANDIA	IND-43468-S-099	07/16/1997		SUBMITTED A NEW STUDY, PN-043, ENTITLED, "PLACEBO-CONTROLLED, DOUBLE-BLINDED TRIAL TO STUDY THE ABSORPTIVE AND POST-ABSORBTIVE SKELETAL MUSCLE AND HEPATIC METABOLIC EFFECTS OF BRL 49653C AFTER 12 WEEKS TREATMENT IN PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS." ALSO SUBMITTED DOCUMENTATION FOR THE FIRST INVESTIGATOR, DR. JOHN GERICH, WHO WILL CONDUCT A STUDY UNDER PN-043. // PHASE-2; TOTAL SYSTEMIC APPEARANCE RATE OF GLUCOSE; POST-PRANDIAL AND FASTING HEPATIC AND MUSCLE GLUCOSE METABOLISM; GLUCONEOGENESIS; NIDDM
SUB	AVANDIA	IND-43468-S-101	07/23/1997		SUBMITTED A NEW PHASE III EXTENSION PROTOCOL, PN-105, ENTITLED, "AN OPEN-LABEL EXTENSION STUDY TO ASSESS THE LONG-TERM SAFETY, TOLERABILITY AND EFFICACY OF BRL 49653C WHEN ADMINISTERED AS MONOTHERAPY, ONCE DAILY, TO PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM)."
SUB	AVANDIA	IND-43468-S-100	07/23/1997		SUBMITTED A NEW PHASE III PROTOCOL, PN-044, ENTITLED, "A 26-WEEK, RANDOMIZED, DOUBLE-BLIND, MULTICENTER, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, SAFETY AND TOLERABILITY OF BRL 49653C WHEN ADMINISTERED TWICE DAILY TO PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS (NIDDM) WHO ARE INADEQUATELY CONTROLLED ON A MAINTENANCE DOSE (2.5 G/DAY) OF METFORMIN."
SUB	AVANDIA	IND-43468-S-102	07/29/1997		SUBMITTED A PROPOSAL FOR NDA QUALIFICATION BATCH STABILITY TESTING. // PHASE-3; TWELVE MONTH STABILITY DATA; THREE MONTH; ICH Q1A GUIDELINES; DRUG PRODUCTL DRUG SUBSTANCE; MATRIX DESIGN

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SUB	AVANDIA	IND-43468-S-103	08/08/1997	INFORMATION AMENDMENT - CHEMISTRY/MICROBIOLOGY PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED NEW PROTOCOL, PN-005, AND DOCUMENTATION FOR THE PRINICPAL INVESTIGATOR, MARTIN FREED. THE PRIMARY OBJECTIVES OF THIS STUDY ARE: (1) TO CHARACTERIZE THE DOSE PROPORTIONALITY OF SINGLE ORAL DOSES OF THE PROPOSED COMMERCIAL TABLET FORMULATION ACROSS A VARIETY OF DOSE LEVELS IN HEALTHY VOLUNTEERS; (2) TO ESTIMATE THE EFFECT OF A HIGH FAT BREAKFAST ON THE PHARMACOKINETICS OF THE FINAL TABLET FORMULATION FOLLOWING A SINGLE ORAL DOSE IN HEALTHY VOLUNTEERS; AND (3) TO ASSESS THE SAFETY AND TOLERABILITY OF SINGLE ORAL DOSES OF THE PROPOSED COMMERCIAL TABLET IN HEALTHY VOLUNTEERS. ALSO SUBMITTED CMC INFORMATION ABOUT FOUR NEW TABLET FORMULATIONS, FORMULA CODES BF, BG, BH AND BJ (1MG, 2MG, 4MG AND 8MG, RESPECTIVELY).
SUB	AVANDIA	IND-43468-S-104	08/11/1997	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED TWO MODIFICATIONS TO PROTOCOLS 082 AND 095 WHICH REPLACE THE TERM "GLUCOMETER" WITH THE GENERIC TERM "GLUCOSE METER" AND RESTATED THE SECONDARY VARIABLES IN ORDER TO CLARIFY SB"S INTENTION TO DESCRIBE THE CHANGE IN TOAL DAILY INSULIN DOSE AND THE PERCENT CHANGE IN INSULIN DAILY DOSAGE FROM BASELINE TO WEEK 26.
SUB	AVANDIA	IND-43468-S-105	08/11/1997	SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-97017827-1.
SUB	AVANDIA	IND-43468-S-106	08/15/1997	INFORMATION AMENDMENT - CLINICAL	SUBMITTED THREE FINAL STUDY REPORTS FOR PROTOCOLS PN-030, PN-034 AND PN-049.
SUB	AVANDIA	IND-43468-S-107	08/15/1997	INFORMATION AMENDMENT - PHARMACOLOGY/TOXICOLOGY	SUBMITTED FOUR PRECLINICAL STUDY REPORTS.
SUB	AVANDIA	IND-43468-S-108	08/18/1997	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED FIRST AMENDMENT TO PROTOCOL 038 WHICH ALLOWS FOR AN INCREASE IN THE TOTAL NUMBER OF SUBJECTS ELIGIBLE FOR STUDY FROM 64 TO 96 AND CORRECTS A TYPOGRAPHICAL ERROR TO REFLECT THE INTENDED REQUIREMENT THAT THE TWO CREATININE MEASUREMENTS USED TO DETERMINE ELIGIBILITY BE OBTAINED AT LEAST TWO WEEKS APART.
SUB	AVANDIA	IND-43468-S-109	08/25/1997	SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-97019410-1.

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SUB	AVANDIA	IND-43468-S-110	08/29/1997	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR TWO NEW INVESTIGATORS, VILLARREAL AND INFANTE, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-044; FOUR NEW INVESTIGATORS, FELICETTA, MAGGIACOMO, MARKUNAS AND SULLIVAN, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-079; SIX NEW INVESTIGATORS, BURKE, DORIN, MCGILL, MITCHELL, NOVECK AND ROTH, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-082; ELEVEN NEW INVESTIGATORS, FARMER, HENRY, HERSHON, KILO, MURRAY, PAOLINO, REDMOND, SUGIMOTO, WEINSTEIN, WILLIAMS AND WINGERT, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-084; ONE NEW INVESTIGATOR, VIETO, TO CONDUCT A STUDY IN ACCORDANCE WITH PN-093; TWELVE NEW INVESTIGATORS, ARIAN, FIRST, BAGDADE, HAAG, MECKLENBURG, PASTER, REYNOLDS, SANT RAM, SJOBERG, SUWANNASRI, TEUTSCH AND TONKENS, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-095; TWELVE NEW INVESTIGATORS, BARRERA, BIDOT, GARLAND, HERBST, KHAIRI, NOVECK, RENDELL, ROSEN, SHARP, TEUTSCH, TONKENS AND WEINSTEIN, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-097; AND FIFTEEN NEW INVESTIGATORS, COLLINS, DELCHER, EARL, FARMER, GARLAND, HENRY, MAGGIACOMO, MILLER, PATRON, ROSENBLOOM, ROSENBLATT, STOKES, WEINSTEIN, WEISS AND ZIGRANG, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-105.
SUB	AVANDIA	IND-43468-S-112	09/03/1997	PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED NEW PROTOCOL, PN-028, AND DOCUMENTATION FOR THE PRINCIPAL INVESTIGATOR, DR. MARTIN FREED.
SUB	AVANDIA	IND-43468-S-111	09/03/1997	SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-97019779-1.
SUB	AVANDIA	IND-43468-S-113	09/04/1997	PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-031, AND DOCUMENTATION FOR A NEW INVESTIGATOR, DR. AZIZ LAURENT.
SUB	AVANDIA	IND-43468-S-114	09/11/1997	PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-041, AND SUPPORTING DOCUMENTATION FOR A NEW INVESTIGATOR, DR. JERRY HERRON.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
MEMO	AVANDIA	IND-43468	09/12/1997		(ELECTRONIC) DOCUMENTS 9/5/97 AND 9/9/97 CONVERSATIONS IN WHICH DALE STOCKBOWER CALLED MIKE JOHNSTON OF THE FDA TO FOLLOW UP ON SB"S REQUEST FOR FDA GUIDANCE ON THE NDA STABILITY PROGRAM FOR BRL 49653, SUBMITTED 7/29/97. NOTED THAT MIKE JOHNSTON, AFTER CONSULTING WITH THE REVIEW CHEMIST, DR. YSERN, INFORMED SB THAT THE PROGRAM IS ADEQUATE AS WRITTEN AND MEETS THE ICH Q1A REQUIREMENTS.
SUB	AVANDIA	IND-43468-S-115	09/12/1997	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR TWENTY-FOUR NEW INVESTIGATORS, BAGDADE, BASKETT, BOWLING, BRUCE, DECHERNEY, FREEMAN, GOVE, GREMILLION, HERBST, HIPPERT, HSI, KLAFF, LEWIN, MORIN, NADEAU, NOVECK, PASTER, REDMOND, RESNICK, REYNOLDS, SCHARYJ, TEUTSCH, TOTH AND WYSHAM, TO CONDUCT STUDIES UNDER PN-105.
SUB	AVANDIA	IND-43468-S-116	09/15/1997	PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-039, AND SUPPORTING DOCUMENTATION FOR A NEW INVESTIGATOR, DR. MARTIN FREED.
SUB	AVANDIA	IND-43468-S-117	09/16/1997	PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED DOCUMENTATION FOR SEVEN NEW INVESTIGATORS, CAGE, DANDONA, FRIED, LUCAS, MULLICAN, OLANSKY AND SIAMI, TO CONDUCT STUDIES UNDER PN-097 AND THIRTEEN NEW INVESTIGATORS, BARRERA, CARLTON, DANDONA, GABRIEL, MATLOCK, MCALLISTER, MILLER, MOORE, MULLICAN, NORTON, SKOBELOFF, SMITH AND TUCKER, TO CONDUCT STUDIES UNDER PN-105.
SUB	AVANDIA	IND-43468-S-118	09/18/1997	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR FIVE NEW INVESTIGATORS, GARBER, LEVIN, PEK, RASKIN AND WOOLF, TO CONDUCT STUDIES UNDER PN-082; ELEVEN NEW INVESTIGATORS, BRODIE, IVERSON, CONRAD, GABRIEL, ISAACSON, MERSEY, MULLICAN, MULMED, PATEL, PORTE AND RASKIN, TO CONDUCT STUDIES UNDER PN-084; ONE NEW INVESTIGATOR, GEWIRTZ, TO CONDUCT A STUDY UNDER PN-090; AND TEN NEW INVESTIGATORS, ANDERSON, BUSCH, GALLINA, GOLAND, HERMAN, HERSHON, ORLANDER, REASNER, BROWN-REUSCH AND STUART, TO CONDUCT STUDIES UNDER PN-095.
SUB	AVANDIA	IND-43468-S-120	09/25/1997	PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-033, AND SUPPORTING DOCUMENTATION FOR A NEW INVESTIGATOR, DR. RALPH DEFRONZO.
SUB	AVANDIA	IND-43468-S-119	09/25/1997	SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-97021527-1.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-121	09/26/1997	INFORMATION AMENDMENT - CLINICAL SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-97021582-1, AND A COPY OF A LETTER SENT TO ALL INVESTIGATORS CONDUCTING CLINICAL STUDIES WITH BRL 49653C.
SUB	AVANDIA	IND-43468-S-122	10/02/1997	PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-112.
SUB	AVANDIA	IND-43468-S-123	10/03/1997	SAFETY REPORT - FOLLOW-UP SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT AE-97022026-1. ALSO SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT AE-97021582-1.
SUB	AVANDIA	IND-43468-S-124	10/13/1997	SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORTS, AE-97021582-1 AND AE-97019410-1, INITIALLY SUBMITTED ON 9/26/97 AND 8/25/97, RESPECTIVELY.
SUB	AVANDIA	IND-43468-S-125	10/27/1997	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR ONE NEW INVESTIGATOR, DOYLE, TO CONDUCT A STUDY IN ACCORDANCE WITH PN-080; THREE NEW INVESTIGATORS, HERBST, ORLANDER AND STUART, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-084; ONE NEW INVESTIGATOR, BEASLEY, TO CONDUCT A STUDY IN ACCORDANCE WITH PN-095; ONE NEW INVESTIGATOR, DOYLE, TO CONDUCT A STUDY IN ACCORDANCE WITH PN-097; SIX NEW INVESTIGATORS, BURGE, CAMP, GRUNBERGER, PHILLIPS, RICHARD AND ROUDEBUSH, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-105; AND TWENTY-NINE NEW INVESTIGATORS, ALWINE, ARONOFF, BERGER, BOWLING, GOVE, GRAF, HERRON, HIGGINS, JAIN, JOHNSTON, KIPNES, LAND, LEFTON, LITTLEJOHN, MERSEY, DICKE, MILLER, MORIN, PASTER, PATRON, PODLECKI, REDMOND, ROSENBLATT, RUDOLPH, SANDALL, STRUTIN, SUWANNASRI, TOFFEL AND WEISS, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-112.
SUB	AVANDIA	IND-43468-S-127	10/28/1997	PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-113, AND DOCUMENTATION FOR THE PRINCIPAL INVESTIGATOR, SHERWYN L. SCHWARTZ.
SUB	AVANDIA	IND-43468-S-126	10/28/1997	SAFETY REPORT - FOLLOW-UP SAFETY REPORT - INITIAL	SUBMITTED INITIAL SAFETY REPORT, AE-97024864-1. ALSO SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORTS, AE-97019410-1 AND AE-9702026-1, INITIALLY SUBMITTED ON 8/25/97 AND 10/13/97, RESPECTIVELY.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
MEMO	AVANDIA	IND-43468	10/31/1997		DOCUMENTS A 10/29/1997 CONVERSATION IN WHICH DR. HERMAN RHEE OF THE FDA MENTIONED SEVERAL POTENTIAL CANDIDATES AND SUGGESTED THAT SB STUDY LOSARTAN. DR. RONALD STEIGERWALT OF THE FDA STATED THAT HE WOULD REVIEW THE HISTOLOGICAL EXAMINATION TECHNIQUES USED IN SB"S CHRONIC TOXICOLOGY STUDIES IN LIGHT OF FAT DEPOSITION IN CARDIAC TISSUE OBSERVED WITH TROGLITAZONE.
SUB	AVANDIA	IND-43468-S-128	11/07/1997	SAFETY REPORT - FOLLOW-UP SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-97025964-1, AND FOLLOW-UP INFORMATION TO SAFETY REPORTS, AE-97021582-1 AND AE-97024864-1, INITIALLY SUBMITTED ON 9/26/1997 AND 10/28/1997, RESPECTIVELY.
SUB	AVANDIA	IND-43468-S-129	11/26/1997	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR THIRTY-EIGHT NEW INVESTIGATORS, AZORR, COLE, CONWAY, DREBOHL, ELI, FIORILLO, GARLAND, GILDERMAN, GILLIE, GOLDSTEIN, HEATLEY, HSI, KLAFF, LACKNER, LIPETZ, MARBURY, MARKUNAS, MILAN, NADEAU, POHL, RAJAN, REDMOND, RENDELL, RIEDERMAN, RIPLEY, ROSENSTOCK, SANT RAM, SCULLY, SHAPIRO, SHELANSKI, STERNER, TANDRON, THRONE, TIDMAN, WAHLEN, WEERASINGHE, WILLIAMS AND WYSHAM, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-113.
SUB	AVANDIA	IND-43468-S-130	12/09/1997	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR ONE NEW INVESTIGATOR, DOYLE, TO CONDUCT A STUDY IN ACCORDANCE WITH PN-080; THREE NEW INVESTIGATORS, CAMP, GOLDSTEIN AND TAM, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-082; FOUR NEW INVESTIGATORS, AMIN, BLONDE, REUSCH AND TAM, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-084; TWO NEW INVESTIGATORS, BEASLEY AND TAM, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-094; ONE NEW INVESTIGATOR, RASKIN, TO CONDUCT A STUDY IN ACCORDANCE WITH PN-095; THREE NEW INVESTIGATORS, BEASLEY, KITABCHI AND MOHAN, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-105; EIGHTEEN NEW INVESTIGATORS, ANDERSON, COHEN, DANDONA, D"ANGELO, DOYLE, DREBOHL, EISENBUD, FELICETTA, GORDON, JOHNSON, LEWIN, MANGIONE, RENDELL, SPISAK, STONE, STRAUSS, TOTH AND WEISMAN, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-112; AND SEVEN NEW INVESTIGATORS, CAOS, ISAACSOHN, BEASLEY, BELL, KERN, MCCARTNEY AND REUSCH, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-113.
SUB	AVANDIA	IND-43468-S-131	12/12/1997	SAFETY REPORT - FOLLOW-UP SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-97028785-1. ALSO SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-97019779-1, INITIALLY SUBMITTED ON 9/3/1997.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-132	12/18/1997	ANNUAL REPORT	SUBMITTED AN ANNUAL REPORT WHICH COVERS THE PERIOD FROM 9/23/1996 THROUGH 9/22/1997.
SUB	AVANDIA	IND-43468-S-133	12/22/1997	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED THE FIRST AMENDMENT TO PROTOCOL 043. NOTED THAT A COMPLETE LISTING OF CHANGES IS PROVIDED.
SUB	AVANDIA	IND-43468-S-134	12/29/1997	INFORMATION AMENDMENT - CLINICAL SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-97029138-1. ALSO SUBMITTED IS A COPY OF THE LETTER SENT TO ALL INVESTIGATORS CONDUCTING CLINICAL STUDIES WITH BRL-49653C UNDER THIS IND.
MEMO	AVANDIA	IND-43468	12/30/1997		(ELECTRONIC) DOCUMENTS A CONVERSATION IN WHICH THE FDA ADVISED THAT THE DIVISION"S POLICY IN REPORTING A PATIENT DEATH IS TO SEND A FAX OUTLINING THE INFORMATION AVAILABLE ON THE CASE, IN LIEU OF A PHONE REPORT. FDA NOTED THAT . THE FAX WILL IMMEDIATELY BE PROVIDED TO THE MEDICAL REVIEWER WHO WOULD THEN DECIDE IF A TELECONFERENCE WOULD BE WARRANTED.
SUB	AVANDIA	IND-43468	12/30/1997	SAFETY 15 DAY SAFETY INITIAL	(FAX) SUBMITTED AN INITIAL 15-DAY ALERT REPORT, AE-97030114-1. NOTED THAT SB CONTACTED THE FDA REGARDING REPORTING THE INCLUDED EVENT AS A 3-DAY TELEPHONE REPORT AND THE FDA DIRECTED SB TO SUBMIT THE EVENT VIA FAX.
SUB	AVANDIA	IND-43468-S-136	01/09/1998	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED SEVERAL MODIFICATIONS TO PROTOCOL 011. A LISTING OF THE AFFECTED SECTIONS WITH THE RATIONALE IS PROVIDED.
SUB	AVANDIA	IND-43468-S-135	01/09/1998	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED ONE NEW INVESTIGATOR, GARLAND, TO CONDUCT A STUDY IN ACCORDANCE WITH PN-011; TWO NEW INVESTIGATORS, GERICH AND SALVATORE, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-084; ONE NEW INVESTIGATOR, SALVATORE, TO CONDUCT A STUDY IN ACCORDANCE WITH PN-090; ONE NEW INVESTIGATOR, STEVENS, TO CONDUCT A STUDY IN ACCORDANCE WITH PN-105; ELEVEN NEW INVESTIGATORS, DAVIS, ENZMANN, GARBER. GOLDBERG, MENEGHINI, GOLDSTEIN, LEICHTER, MCGILL, PONTE, PORTE AND RICHARDSON, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-112; AND NINE NEW INVESTIGATORS, CLINKINGBEARD, FISHER, MILLER, NEUTEL, PHILLIPSON, RASKIN, SNYDER, SPERLING AND TAM, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-113. ALSO SUBMITTED REVISIONS TO AN INVESTIGATOR PREVIOUSLY SUBMITTED UNDER PN-105.
SUB	AVANDIA	IND-43468-S-137	01/12/1998	INFORMATION AMENDMENT - CLINICAL SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-97030114-1, AND A COPY OF THE LETTER WHICH INFORMED THE INVESTIGATORS OF THE ADVERSE EXPERIENCE, HYPOGLYCEMIC CARDIAC ARREST.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-138	01/14/1998	INFORMATION AMENDMENT - CLINICAL SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-97030114-1, INITIALLY SUBMITTED ON 1/12/1998. ALSO SUBMITTED A REVISED COPY OF A LETTER SENT TO ALL INVESTIGATORS CONDUCTING CLINICAL STUDIES WITH BRL 49653C TO INCLUDE THE ADDITION OF THE SENTENCE: "AN ECG SHOWED NO EVIDENCE OF ACUTE ISCHEMIA OR INFARCTION" AND A SPELLING CORRECTION TO HYPERCHOLESTEROLEMIA.
SUB	AVANDIA	IND-43468-S-139	01/23/1998	INFORMATION AMENDMENT - CLINICAL	SUBMITTED FINAL CLINICAL REPORT FOR PN-040.
SUB	AVANDIA	IND-43468-S-140	01/26/1998	INFORMATION AMENDMENT - PHARMACOLOGY/TOXICOLOGY	SUBMITTED THIRTEEN PRECLINICAL REPORTS, BF-1022, BF-1015, BF-1025, RSD-100LX0/1, RSD-100D7C/1, RSD-100LL1/1, RSD-1005R1/1, RSD-100K5D/1, RSD-100HKW/1, RSD-100M82/2, RSD-100KNN/1, RSD-100LJ7/1 AND RSD-100L40/1.
MEMO	AVANDIA	GENERAL	01/26/1998		DOCUMENTS A CONVERSATION IN WHICH THE FDA SHARED SOME SPECIFIC M&E DIVISIONAL GUIDANCE WITH SB: THE FDA PREFERS THE ISS AND ISE TO BE SUMMARY DOCUMENTS OF ABOUT 100 PAGES IN LENGTH WITH SUPPORTING DATA CROSS-REFERENCED TO OTHER SECTIONS OF THE NDA; ALL OF SB"S QUESTIONS FOR THE PRE-NDA MEETING SHOULD BE PRESENTED ON OVERHEADS; AND MIKE JOHNSTON OF THE FDA WILL SEND A WEEKLY UPDATE OF THE NDA REVIEW STATUS VIA E-MAIL.
MEMO	AVANDIA	IND-43468	01/26/1998		DOCUMENTS A CONVERSATION IN WHICH THE FDA INFORMED SB THAT A NEW STATISTICAL REVIEWER HAS NOT BEEN ASSIGNED YET BUT ED NEVIUS HAS BEEN ASSIGNED TO THE IND IN THE INTERIM. NOTED THAT SB INFORMED THE FDA THAT THEY ARE PLANNING FOR A PRE-NDA MEETING IN LATE MARCH OR EARLY APRIL.
SUB	AVANDIA	IND-43468-S-141	01/27/1998	PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL PN-114.
SUB	AVANDIA	IND-43468-S-142	01/28/1998	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR TWO NEW INVESTIGATORS, BEASLEY AND GARLAND, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-024; ONE NEW INVESTIGATOR, GARLAND, TO CONDUCT A STUDY IN ACCORDANCE WITH PN-084; TWO NEW INVESTIGATORS, GARLAND AND SCHWARTZ, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-094; TWO NEW INVESTIGATORS, ADAMS AND WOOL, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-112; AND TWO NEW INVESTIGATORS, DOYLE AND FONSECA, TO CONDUCT STUDIES IN ACCORDANCE WITH PN-113. ALSO SUBMITTED REVISED DOCUMENTATION FOR INVESTIGATORS PREVIOUSLY SUBMITTED UNDER PN-105, PN-112 AND PN-113.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-143	02/05/1998	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED,TO PROTOCOLS 082 AND 095, THE SECOND MODIFICATION WHICH PROVIDES FOR A CHANGE IN THE DEFINITION OF HBA1C RESPONDERS. NOTED THAT A LIST OF REVISIONS AND REVISED PROTOCOLS ARE PROVIDED.
SUB	AVANDIA	IND-43468-S-144	02/09/1998	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED A MODIFICATION TO PROTOCOL 090 WHICH REMOVES THE ANALYSIS OF RESPONDER RATE WITH RESPECT TO HBA1C. NOTED THAT A LIST OF THE AFFECTED PROTOCOL SECTIONS AND A COPY OF THE REVISED PROTOCOL IS PROVIDED.
SUB	AVANDIA	IND-43468-S-145	02/13/1998	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED SITE REVISIONS FOR INVESTIGATORS PARTICIPATING IN PROTOCOLS 079, 080, 082, 084, 090, 093, 094, 095, 096, 097, 105 AND 113.
SUB	AVANDIA	IND-43468-S-146	03/16/1998	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED SEVERAL MODIFICATIONS TO PROTOCOL 024. PROVIDED A LIST OF THE AFFECTED SECTIONS AND THE RATIONALE FOR THE MODIFICATIONS.
SUB	AVANDIA	IND-43468-S-147	03/18/1998	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR ONE NEW INVESTIGATOR, DOYLE, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-079; ONE NEW INVESTIGATOR, GARLAND, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-080; ONE NEW INVESTIGATOR, GLATTE, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-093; ONE NEW INVESTIGATOR, BEASLEY, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-097; TWO NEW INVESTIGATORS, GRUNBERGER AND LEVIN, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-112; FIVE NEW INVESTIGATORS, BUSICK, GLATTE, QUINONES, ROMAN AND CRANDALL, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-113; AND NINETEEN NEW INVESTIGATORS, ARONOFF, BOWLING, BUSCH, COLE, ENZMAN, EVANS, GRAF, HERSHON, JAIN, KILO, KLAFF, LEWIN, MARBURY, MORIN, PODLECKI, ROSENSTOCK, STOKES, STONE AND WYSHAM, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-114.
MEMO	AVANDIA	GENERAL	03/20/1998		MATT WHITMAN OF SB INFORMED THE AVANDIA TEAM OF THE FDA"S AVAILABILITY FOR A PRE-NDA MEETING AND REQUESTED EACH PERSON"S AVAILABILITY.
SUB	AVANDIA	IND-43468-S-148	03/23/1998	SAFETY FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-1997030114-1.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-149	03/27/1998	OTHER	SB REQUESTED A PRE-NDA MEETING WITH THE FDA TO DISCUSS SB"S PLANS FOR AN NDA SUBMISISON IN DECEMBER 1998 FOR ROSIGLITAZONE TABLETS FOR THE TREATMENT OF TYPE 3 DIABETES BOTH AS MONOTHERAPY AND IN COMBINATION WITH SULPHONYUREAS AND METFORMIN. NOTED THAT SB IS PLANNING TO FILE A SECOND NDA IN EARLY 199 WHICH WOULD BE COMPOSED PRIMARILY OF THE CLINICAL STUDIES EXAMINING COMBINATION USE OF ROSIGLITAZONE AND INSULIN.
SUB	AVANDIA	IND-43468	03/31/1998	SAFETY 10 DAY SAFETY INITIAL	(FAX) SUBMITTED AN INITIAL 10-DAY ALERT REPORT, AE-1998007684-1. NOTED THAT THE INVESTIGATOR CONSIDERED THIS EVENT TO BE POSSIBLY RELATED TO STUDY MEDICATION.
SUB	AVANDIA	IND-43468-S-150	04/03/1998	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED MODIFICATIONS TO PROTOCOLS 094 AND 093. NOTED THAT A LISTING OF THE MODIFICATIONS IS PROVIDED, FOLLOWED BY A COMPLETE COPY OF THE REVISED PROTOCOLS.
SUB	AVANDIA	IND-43468-S-151	04/09/1998	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR TWO NEW INVESTIGATORS, SYNDER AND HAAG, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH 095; AND DOCUMENTATION FOR THIRTY-FIVE NEW INVESTIGATORS, AHMANN, BEASLEY, BLOCK, BURNETT, CAMP, COLLINS, CONWAY, DECHERNEY, DELCHER, DONOVAN, DORIN, FARMER, GORE, HIGGINS, LACAVA, LEVIN, MARKUNAS, MECKLENBERG, MILLER, NOVECK, PASTER, RENDELL, REYNERTSON, REYNOLDS, RIDDLE, ROSENBLOOM, ROTH, SCHWARTZ, SJOBERG, SMITH, SORENSON, SUWANNASRI, TONKENS, TOTH AND WOOLF, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-114.
SUB	AVANDIA	IND-43468-S-153	04/16/1998	OTHER	SUBMITTED A BRIEFING DOCUMENT FOR THE 4/30/1998 PRE-NDA MEETING.
SUB	AVANDIA	IND-43468-S-152	04/16/1998	SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO 7-DAY FAX REPORT, AE-1998007684-1, INITIALLY SUBMITTED ON 03/31/1998.
SUB	AVANDIA	IND-43468-S-154	04/22/1998	OTHER	SUBMITTED AN ADDENDUM TO THE PRE-NDA MEETING BRIEFING DOCUMENT WHICH PROVIDES FOR INITIAL CLINICAL DATA FROM THE PHASE III PIVOTAL STUDY 011.
CFF	AVANDIA	GENERAL	04/23/1998		(ELECTRONIC) FDA PROVIDED A LIST OF THE FDA ATTENDEES FOR THE 4/30/1998 PRE-NDA MEETING.
SUB	AVANDIA	IND-43468-S-155	04/24/1998	INFORMATION AMENDMENT - CLINICAL SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-1998009607-1, AND A COPY OF THE LETTER WHICH INFORMED INVESTIGATORS OF THE ADVERSE EXPERIENCES, CONGESTIVE HEART FAILURE AND DECREASE IN RED CELL PARAMETERS.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-156	05/08/1998	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR ONE NEW INVESTIGATOR, TABER, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-084; DOCUMENTATION FOR ONE NEW INVESTIGATOR, GORAL, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-105; DOCUMENTATION FOR THREE NEW INVESTIGATORS, MEZITIS, TABER AND WITTLIN, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-113; AND DOCUMENTATION FOR SEVEN NEW INVESTIGATORS, ANDERSON, GALLINA, GOLDSTEIN, HAAG, MCGILL, ORLANDER AND REUSCH, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-114.
SUB	AVANDIA	IND-43468-S-157	05/15/1998	INFORMATION AMENDMENT - PHARMACOLOGY/TOXICOLOGY	SUBMITTED THREE PRECLINICAL REPORTS, BRL-049653/RSD-100N22/1, BRL-049653/RSD-100JSC/2 AND PF-1006/BRL-049653/2. NOTED THAT PF-1006/BRL-049653/2 WAS PREVIOUSLY SUBMITTED ON 3/15/1996 BUT HAS SINCE BEEN REVISED.
MEMO	AVANDIA	IND-43468	05/15/1998		DOCUMENTS A CONVERSATION IN WHICH THE FDA STATED THAT THERE IS NO STRONG PREFERENCE IN THE DIVISION FOR ONE OPTION OVER THE OTHER REGARDING FILING STRATEGY (MONTHERAPY VERSUS COMBINATION TREATMENT). FDA NOTED THAT WHILE THE INITIAL NDA IS UNDER REVIEW, ANY SUBSEQUENT NDA SUBMISSIONS WOULD NOT BE CONSIDERED EFFICACY SUPPLEMENTS AND THAT THEY WILL BE CONSIDERED A FULL NDA REGARDLESS OF THE NUMBER OF INDICATIONS INCLUDED IN IT.
SUB	AVANDIA	IND-43468-S-158	05/20/1998	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED THE FIRST AMENDMENT TO PROTOCOL 105 WHICH EXTENDS THE STUDY TREATMENT PERIOD FROM 12 MONTHS TO 24 MONTHS.
MEMO	AVANDIA	IND-43468	05/26/1998		MARK LEWIS OF SB NOTED THAT, DUE TO AN ERROR IN PHOTOCOPYING, SOME PAGES OF THE REPORT FOR STUDY TF-1041/BRL-049653/2 ARE MISSING AND PROVIDED A COPY OF PAGES 33-33.
SUB	AVANDIA	IND-43468-S-159	05/29/1998	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED THE SECOND MODIFICATION TO PROTOCOL 096 WHICH PROVIDES FOR A CHANGE IN THE DEFINITION OF HBA1C RESPONDER TO REFLECT THE FDA DRAFT GUIDELINE FOR EVALUATION OF NEW TREATMENTS FOR DIABETES MELLITUS.
SUB	AVANDIA	IND-43468-S-160	06/02/1998	OTHER	SUBMITTED A COPY OF SB"S MINUTES FROM THE 4/30/1998 PRE-NDA MEETING WITH THE FDA AND REQUESTED A COPY OF THE FDA"S MEETING MINUTES.
SUB	AVANDIA	IND-43468	06/29/1998		SUBMITTED HOUSE ORGANS AV981G-GA AND AV982G-GA, DISPLAYED AT THE AMERICAN DIABETES ASSOCIATION MEETING IN CHICAGO, ILLINOIS ON 6/13/1998.

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SUB	AVANDIA	IND-43468-S-163	07/09/1998	INFORMATION AMENDMENT - CLINICAL SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-1998016250-1, AND A COPY OF THE LETTER WHICH INFORMED THE INVESTIGATORS OF THE ADVERSE EXPERIENCE, GYNECOMASTIA.
SUB	AVANDIA	IND-43468-S-162	07/10/1998	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR ONE NEW INVESTIGATOR, NUNEZ, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-084; DOCUMENTATION FOR ONE NEW INVESTIGATOR, NUNEZ, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-095; DOCUMENTATION FOR ONE NEW INVESTIGATOR, NUNEZ, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-10; AND DOCUMENTATION FOR EIGHT NEW INVESTIGATORS, BARRERA, DONOVAN, GARBER, HERMAN, NUNEZ, PEK, RASKIN AND REASNER, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-114.
SUB	AVANDIA	IND-43468-S-161	07/20/1998	INFORMATION AMENDMENT - CLINICAL	SUBMITTED THE FINAL CLINICAL REPORT FOR STUDY PN-006. NOTED THAT THE ENTIRE SUBMISSION WAS PROVIDED IN ELECTRONIC FORMAT CONFORMING TO THE 4/8/1998 DRAFT GUIDELINES ON ELECTRONIC SUBMISSIONS.
SUB	AVANDIA	IND-43468-S-164	07/29/1998	SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-1998016250-1, INITIALLY SUBMITTED ON 7/9/1998.
SUB	AVANDIA	IND-43468-S-165	07/31/1998	INFORMATION AMENDMENT - CLINICAL	SUBMITTED THE FINAL CLINICAL REPORT FOR PN-107.
MEMO	AVANDIA	IND-43468	07/31/1998		DOCUMENTS A CONVERSATION IN WHICH BOB MISBIN OF THE FDA NOTED THAT HE IS TO BE THE MEDICAL REVIEWER FOR THE AVANDIA NDA AND REQUESTED A SMALL INFORMAL MEETING ON CLINICAL DATA AND FILING PLANS FOR 8/13/1998. FDA NOTED THEIR INTEREST IN THE LIVER SAFETY PROFILE OF AVANDIA AND SB"S PLAN TO FILE THE UNIQUE INDICATION OF A GLITAZONE + METFORMIN IN THE FIRST NDA.
MEMO	AVANDIA	IND-43468	08/01/1998		(ELECTRONIC) DOCUMENTS A CONVERSATION IN WHICH THE FDA REQUESTED AN INFORMAL MEETING ON 08/13/1998 TO DISCUSS CLINICAL DATA AND FILING PLANS. NOTED THAT THE LIVER SAFETY PROFILE PLUS SB"S PLAN TO FILE THE UNIQUE INDICATION OF A GLITAZONE+METFORMIN IN THE FIRST NDA PROVIDES THE FDA WITH TWO BASES TO SEEK PRIORITY REVIEW.
SUB	AVANDIA	IND-43468-S-166	08/04/1998		(FAX) SUBMITTED A COPY OF THE 8/4/1998 IND-43468-S-166 SUBMISSION REQUESTING A MEETING TO DISCUSS AN ELECTRONIC NDA SUBMISSION.

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SUB	AVANDIA	IND-43468-S-166	08/04/1998	OTHER	SUBMITTED A REQUEST FOR A MEETING TO DISCUSS SB"S PLANS FOR AN ELECTRONIC NDA. NOTED THAT SB INTENDS TO COMPLY WITH THE 4/8/1998 DRAFT GUIDELINES BUT REQUESTED THE FDA"S INPUT ON SEVERAL ISSUES REGARDING THE ELECTRONIC SUBMISSION.
MEMO	AVANDIA	GENERAL	08/14/1998		CLARE KAHN PROVIDED MINUTES OF THE 8/13/1998 AVANDIA MEETING BETWEEN DAVID WHEADON, JAI PATEL, ELIZABETH RAPPAPORT AND CLARE KAHN OF SB AND THE FDA.
MEMO	AVANDIA	IND-43468	08/19/1998		DOCUMENTS A CONVERSATION IN WHICH ALEXANDER FLEMING OF THE FDA INFORMED SB THAT HE WAS LEAVING THE FDA AT THE END OF AUGUST. NOTED THAT SB REQUESTED THAT FDA EXPLAIN THE EXACT CONSTRUCT OF THE COMBINED DATA THAT SUPPORT THE SINGLE SAFETY TABLE IN THE REZULIN LABEL AS THE NUMBERS IN THE REZULIN AND PLACEBO COLUMNS DO NOT ADD UP TO WHAT IS FOUND IN THE SBA. ALSO NOTED THAT SB ASKED DR. FLEMING HIS VIEWS ABOUT CONSULTING FOR SB ON THE AVANDIA PROJECT.
SUB	AVANDIA	IND-43468-S-167	08/20/1998	INFORMATION AMENDMENT - CLINICAL	SUBMITTED THE FINAL CLINICAL REPORT FOR STUDY PN-008.
SUB	AVANDIA	IND-43468-S-168	08/20/1998	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR ONE NEW INVESTIGATOR, BAGDADE, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-114.
SUB	AVANDIA	IND-43468-S-169	09/04/1998	SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-1997030114-1, INITIALLY SUBMITTED ON 1/12/1998.
SUB	AVANDIA	IND-43468-S-170	09/18/1998	ANNUAL REPORT	SUBMITTED AN ANNUAL REPORT WHICH COVERS THE PERIOD FROM 9/23/1997 THROUGH 6/18/1998. NOTED THAT THE REPORTING PERIOD IS NINE MONTHS SO THAT ONE CLINICAL CUT-OFF DATE IS BEING USED FOR SB"S DECEMBER 1998 NDA SUBMISSION.
SUB	AVANDIA	IND-43468-S-171	09/21/1998	INFORMATION AMENDMENT - CLINICAL	SUBMITTED THE FINAL CLINICAL REPORT FOR STUDY 041.
SUB	AVANDIA	IND-43468-S-172	09/29/1998	SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-1998023377-1, AND A COPY OF THE LETTER WHICH INFORMED THE INVESTIGATORS OF THE ADVERSE EXPERIENCE, HEMOLYTIC ANEMIA.
SUB	AVANDIA	IND-43468-S-173	10/05/1998	PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-116, AND DOCUMENTATION FOR ONE NEW INVESTIGATOR, DR. JONATHAN C. FOX, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-116.
SUB	AVANDIA	IND-43468-S-174	10/13/1998	PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-127.

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SUB	AVANDIA	IND-43468-S-175	10/20/1998	SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-1998023377-1, INITIALLY SUBMITTED ON 9/29/1998.
MEMO	AVANDIA	IND-43468	10/27/1998		DOCUMENTS A CONVERSATION IN WHICH THE FDA PROVIDED COMMENTS ON PROTOCOL 127. NOTED THAT THE FDA EXPRESSED THEIR CONCERN ABOUT ALLOWING PATIENTS TO REMAIN HYPERGLYCEMIC FOR SIX MONTHS IN STUDY 127. ALSO NOTED THAT THE FDA INQUIRED AS TO WHETHER SB HAS PHASE IIIB PLANS FOR IMPARIED GLUCOSE TOLERANCE (IGT) STUDIES AND A LIVER TOXICITY STUDY.
SUB	AVANDIA	IND-43468-S-177	11/02/1998	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR ELEVEN NEW INVESTIGATORS, BOWLING, COLE, DELCHER, EARL, HERRON, HSI, KAPLAN, ROSENSTOCK, ROSENTHAL, SALVATORE AND WEISS, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-127.
SUB	AVANDIA	IND-43468-S-178	11/03/1998	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED AN AMENDED PROTOCOL PN-116 WHICH PROVIDES FOR CHANGES IN THE TERTIARY OBJECTIVE OF THE STUDY, CPU STAY TIME AND DOSAGE SCHEDULE.
SUB	AVANDIA	IND-43468-S-176	11/04/1998	INFORMATION AMENDMENT - CLINICAL	SUBMITTED FINAL CLINICAL REPORTS FOR THREE PHASE III STUDIES, PN-011, PN-020 AND PN-024. NOTED THAT THE COMPLETE SUBMISSION IS BEING PROVIDED IN PDF AND THE CRTS AND LINE LISTINGS ARE AVAILABLE IN ELECTRONIC FORMAT ONLY.
MEMO	AVANDIA	IND-43468 NDA-21071	11/05/1998		DOCUMENTS A CONVERSATION IN WHICH THE FDA ASSIGNED USER FEE ID 3590 AND APPLICATION NUMBER, NDA-21071, TO AVANDIA.
SUB	AVANDIA	IND-43468-S-179	11/20/1998	PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED NEW PROTOCOL, PN-109, AND DOCUMENTATION FOR TWO NEW INVESTIGATORS, LEBOVITZ AND BANERJI, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-109.
SUB	AVANDIA	IND-43468-S-180	11/20/1998	PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED NEW PROTOCOL, PN-131, AND DOCUMENTATION FOR TWO NEW INVESTIGATORS, LEBOVITZ AND BANERJI, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-131.
SUB	AVANDIA	NDA-21071	11/24/1998	ORIGINAL APPLICATION	SUBMITTED A NEW DRUG APPLICATION FOR AVANDIA IN THE TREATMENT OF HYPERGLYCEMIA OF TYPE 2 DIABETES AS MONOTHERAPY AND IN COMBINATION WITH METFORMIN (COADMINISTRATION). NOTED THAT SB HAS REQUESTED A PRIORITY REVIEW BASED ON LIVER SAFETY AND NOVEL INDICATION.
SUB	AVANDIA	IND-43468-S-181	11/25/1998	INFORMATION AMENDMENT - CLINICAL SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-1998026662-1, AND A COPY OF THE LETTER WHICH INFORMED THE INVESTIGATORS OF THE ADVERSE EXPERIENCE, RESPIRATORY FAILURE.

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SUB	AVANDIA	IND-43468-S-182	12/02/1998	INFORMATION AMENDMENT - CLINICAL SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-1998026662-1, INITIALLY SUBMITTED ON 11/25/998. ALSO SUBMITTED A COPY OF THE LETTER WHICH INFORMED THE INVESTIGATORS OF THE ADVERSE EXPERIENCE, RESPIRATORY FAILURE.
SUB	AVANDIA	IND-43468-S-183	12/11/1998	PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-121, AND DOCUMENTATION FOR ONE NEW INVESTIGATOR, JONATHAN C. FOX, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-121.
SUB	AVANDIA	NDA-21071	12/17/1998		SUBMITTED, IN RESPONSE TO THE FDA"S 12/3/1998 AND 12/4/1998 REQUESTS, TABULAR LISTINGS OF INVESTIGATOR NAMES AND ADDRESSES BY CENTER NUMBER, TABULAR SUMMARIES OF PATIENT DISPOSITION BY CENTER, REASONS FOR STUDY CONCLUSION AND A LISTING OF PATIENTS EXCLUDED FROM EFFICACY ANALYSES FOR PIVOTAL STUDIES PN-011, PN-020, PN-024, PN-093 AND PN-094.
SUB	AVANDIA	IND-43468-S-185	12/18/1998	INFORMATION AMENDMENT - CLINICAL	SUBMTTED THE FINAL CLINICAL REPORT FOR STUDY PN-005.
SUB	AVANDIA	IND-43468-S-184	12/18/1998	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED, TO PROTOCOL 127, AMENDMENTS 1 AND 2 WHICH PROVIDE FOR CHANGES IN THE UPPER LIMIT OF FASTING PLASMA GLUCOSE (FPG) AND INCLUSION CRITERIA. NOTED THAT A SAFETY SUMMARY OF EMERGING DATA FROM PHASE II CLINICAL TRIALS IS ATTACHED.
SUB	AVANDIA	NDA-21071	12/28/1998		(FAX) PROVIDED CLARIFICATION OF LAB TRANSITIONS IN THE ISS FOR AVANDIA.
SUB	AVANDIA	IND-43468-S-186	12/29/1998	INFORMATION AMENDMENT - CLINICAL SAFETY REPORT - INITIAL	SUBMITTED AN INITIAL SAFETY REPORT, AE-1998030137-1, AND A COPY OF THE LETTER WHICH INFORMED THE INVESTIGATORS OF THE ADVERSE EXPERIENCES, BILATERAL HYDRONEPHROSIS AND ACUTE RENAL FAILURE.
SUB	AVANDIA	IND-43468-S-187	12/30/1998	SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-1998026662-1, INITIALLY SUBMITTED ON 11/25/1998.
SUB	AVANDIA	NDA-21071	01/05/1999		FAX) PROVIDED, IN RESPONSE TO THE FDA"S 1/4/1999 REQUEST, REVISED INVESTIGATOR TABLES FOR THE FIVE PIVOTAL STUDIES SUPPORTING NDA-21071, PN-011, PN-020, PN-024, PN-093 AND PN-094.
MEMO	AVANDIA	NDA-21071	01/08/1999		DOCUMENTS A CONVERSATION IN WHICH THE FDA RAISED QUESTIONS REGARDING THE ISS AND REQUESTED A TELECONFERENCE WITH THE ISS AUTHORS AND A STATISTICIAN. NOTED THAT A TELECONFERENCE WAS SCHEDULED FOR 1/13/1999.

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MEMO	AVANDIA	NDA-21071	01/08/1999		DOCUMENTS A CONVERSATION IN WHICH THE FDA NOTED THAT THE NDA REVIEW TEAM WILL MEET ON 1/20/1999 TO DETERMINE THE FILING ACCEPTABILITY, REVIEW STATUS AND NEED FOR AN ADVISORY COMMITTEE MEETING. NOTED THAT SB INFORMED THE FDA THAT THEY WOULD BE ABLE TO MEET THE 3/25/1999 - 3/26/1999 ADVISORY COMMITTEE MEETING IF A SPOT WAS OFFERED.
SUB	AVANDIA	NDA-21071	01/11/1999	AMENDMENT TO PENDING APPLICATION	SUBMITTED A REPLACEMENT PAPER COPY OF ITEM 3 SUMMARY, VOLUME 1.3.001 FROM THE ORIGINAL 11/25/1998 NDA SUBMISSIONS. NOTED THAT CHANGES WERE MADE IN THE ANNOTATED LABELING, PRECLINICAL SUMMARY AND HUMAN PHARMACOKINETICS SUMMARY.
MEMO	AVANDIA	NDA-21071	01/12/1999		(ELECTRONIC) DOCUMENTS A CONVERSATION IN WHICH THE FDA REQUESTED CLARIFICATION OF THE CFN NUMBER AND ADDRESS FOR THE CORK FACILITY. NOTED THAT SB ASSURED THE FDA THAT THE CFN NUMBER PROVIDED, WHICH IS A COMBINATION OF LETTERS AND NUMBERS (FCEI053) WAS ISSUED BY THE FDA, AND THAT THE ADDRESS PROVIDED IS THE OFFICIAL ADDRESS LISTED WITH FDA, EVEN THOUGH IT IS DOES NOT CONTAIN A STREET NUMBER.
SUB	AVANDIA	IND-43468-S-188	01/14/1999	SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-1998026662-1, INITIALLY SUBMITTED ON 11/25/1998.
SUB	AVANDIA	IND-43468-S-188	01/14/1999	SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-1998026662-1, INITIALLY SUBMITTED ON 11/25/1998.
SUB	AVANDIA	NDA-21071	01/15/1999		SUBMITTED SAS TRANSPORT FILES, RELATED DOCUMENTATION AND LISTING FILES, PROC CONTENTS LISTING AND PROC PRINT LISTINGS FOR THE FOLLOWING PHASE II/ PHASE III STUDIES: PN-006, PN-009, PN-011, PN-015, PN-020, PN-024, PN-079, PN-080, PN-084, PN-090, PN-091, PN-093, PN-094, PN-096, PN-097, PN-098, PN-105, PN-112 AND PN-113.
SUB	AVANDIA	IND-43468-S-189	01/19/1999	PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-133.
SUB	AVANDIA	IND-43468-S-190	01/20/1999	PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR THREE NEW INVESTIGATORS, HALLE, MAHEUX AND WOO, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-044; AND TWELVE NEW INVESTIGATORS, DOYLE, EDWARDS, FISH, GOLDSTEIN, GROCH, HYMAN, HALLE, LEITER, MAHEUX, TAM, TILDESLEY AND WARREN, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-127.

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MEMO	AVANDIA	NDA-21071	01/21/1999		DOCUMENTS A CONVERSATION IN WHICH THE FDA NOTED THE FOLLOWING: AVANDIA HAS BEEN LOGGED IN FOR REVIEW; A 6-MONTH PRIORITY REVIEW STATUS HAS BEEN GRANTED WITH AN ACTION DATE OF 5/25/1999; THERE WILL BE AN ADVISORY COMMITTEE (ADCOM) MEETING ON 4/23/1999 OR 5/7/1999; THE REVIEW OF EFFICACY DATA IS UNDERWAY AND THERE IS A FAVORABLE IMPRESSION; AND THE PRELIMINARY SAFETY REVIEW WAS COMPLETED THE PREVIOUS WEEK. NOTED THAT FDA REQUESTED THAT SB PROVIDE DATA AND PERMISSION TO THE FDA TO PRESENT LIVER SAFETY DATA IN AVANDIA AT THE 3/26/1999 REZULIN ADCOM MEETING.
SUB	AVANDIA	NDA-21071	01/28/1999		SUBMITTED, IN RESPONSE TO THE FDA"S 1/8/1999 REQUEST, ADDITIONAL INFORMATION FOR THE FOLLOWING INVESTIGATOR STUDY SITES: STUDY 011, DR, ANDREW LEWIN, CENTER 007; STUDY 024, DR. JEFFREY HERBST, CENTER 052; STUDY 093, DR. JAMES SYNDER, CENTER 033; AND STUDY 094, DR. JACK WAHLEN, CENTER 007. NOTED THAT THE FOLLOWING INFORMATION IS PROVIDED FOR EACH STUDY: 1572 FORM; COPY OF THE PROTOCOL AND AMENDMENTS; TOTAL NUMBER OF PATIENTS RANDOMIZED AND COMPLETED; LIST OF DROPOUTS AND REASONS FOR WITHDRAWAL; LIST OF ADVERSE EVENTS FOR ALL PATIENTS; A COPY OF ALL SIGNED INFORMED CONSENT DOCUMENTS; AND THE IDENTIFIED CASE REPORT FORMS.
SUB	AVANDIA	IND-43468-S-191	01/29/1999	SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-1997030114-1, INITIALLY SUBMITTED ON 1/12/1998.
CFF	AVANDIA	NDA-21071	02/02/1999		(FAX) FDA REQUESTED ADDITIONAL INFORMATION REGARDING THE DISSOLUTION MEDIA, ASSAY VALIDATION DATA FOR STUDIES WHERE CONCENTRATION OF DRUGS OTHER THAN ROSIGLITAZONE WERE DETERMINED AND VALIDATION DATA FOR ALL ASSAY METHODS USED IN THE RADIOLABEL STUDY, PN-049.
MEMO	AVANDIA	NDA-21071	02/03/1999		DOCUMENTS A CONVERSATION IN WHICH THE FDA REQUESTED MORE INFORMATION ON THE SPECIAL TOXICOLOGY STUDIES OF LIVER EFFECTS COMPARING ROSIGLITAZONE TO TROGLITAZONE METABOLITES THAT WERE REFERENCED IN ITEM 3E (SECTION 3.7.3).
SUB	AVANDIA	NDA-21071	02/03/1999		(FAX) SUBMITTED THE ITEM 3E SUMMARY PAGES FROM THE SPECIAL TOXICOLOGY STUDIES PERTAINING TO LIVER EFFECTS. NOTED THAT SB INQURIED AS TO WHETHER THE FDA WOULD LIKE OTHER SPECIAL TOXICOLOGY STUDY SUMMARIES.
SUB	AVANDIA	NDA-21071	02/04/1999		SUBMITTED RAT AND MOUSE CARCINOGENICITY STUDY DATA SETS.

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SUB	AVANDIA	IND-43468-S-192	02/04/1999	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED, TO PN-112, AMENDMENT 2 WHICH INCREASES THE DOSE OF BRL-49653C IN ORDER TO OBTAIN ADDITIONAL EFFICACY, SAFETY AND TOLERABILITY DATA OF BRL-49653C AT A TOTAL DAILY DOSE OF 8 MG WHEN ADMINISTERED IN COMBINATION WITH A SULFONYLUREA.
CFF	AVANDIA	NDA-21071	02/05/1999		(FAX) FDA PROVIDED A LIST OF FIGURES AND TABLES FROM THE ISS AND ISE AND STUDIES 011, 024, 020, 094 AND 096 AND REQUESTED AN ELECTRONIC COPY OF THIS DATA ON DISKETTE. FDA ALSO REQUESTED ADDITIONAL INFORMATION ON LIVER CASES 105.022.60245, 006.003.00349 AND 091.206.80319.
MEMO	AVANDIA	NDA-21071	02/08/1999		DOCUMENTS A CONVERSATION IN WHICH THE FDA REQUESTED SUMMARY INFORMATION ON THE SPECIAL TOXICOLOGY STUDIES OF LIVER EFFECTS COMPARING ROSIGLITAZONE AND TROGLITAZONE METABOLITES. DR. MISBIBN ALSO INDICATED THAT HE COMPILED A LIST OF 29 TABLES.FIGURES FROM THE NDA THAT HE WOULD LIKE ON DISKETTE.
MEMO	AVANDIA	NDA-21071	02/09/1999		DOCUMENTS A CONVERSATION IN WHICH THE FDA SCHEDULED THE ADVISORY COMMITTEE MEETING FOR AVANDIA FOR 4/22/1999.
SUB	AVANDIA	NDA-21071	02/16/1999		SUBMITTED, IN RESPONSE TO THE FDA"S 2/2/1999 REQUEST, THE FOLLOWING INFORMATION IN TABULAR FORMAT FOR PIVOTAL STUDIES 011, 024, 093 AND 094: PROTOCOL NUMBER; SITE/CENTER NUMBER; NAME AND ADDRESS OF THE PRINCIPAL INVESTIGATOR AND SITE; NAME AND ADDRESS OF THE MONITORING ORGANIZATION AND TYPE; NAME OF THE MONITOR AND DATES OF MONITORING RESPONSIBILITY; AND A YES/NO ANSWER REGARDING WHETHER ORIGINAL SUBJECT DOCUMENTS WERE REVIEWED DURING THE MONITORING VISIT. ALSO SUBMITTED A COPY OF THE MONITORING SOP USED AT EACH SITE.
MEMO	AVANDIA	NDA-21071	02/17/1999		(ELECTRONIC) DISTRIBUTED ONE FDA CONVERSATION RECORD CONCERNING ELECTRONIC SUBMISSION AND STATUS OF CMC REVIEW. \\ PARENT
MEMO	AVANDIA	NDA-21071	02/17/1999		(ELECTRONIC) DOCUMENTS A MEETING BETWEEN DALE STOCKBOWER AND JOHN WOJCIK OF SB AND THE FDA IN WHICH SB ASSISTED DR. YSERN IN LOADING THE AVANDIA ELECTRONIC NDA ON HIS DESKTOP, AND PROVIDED TRAINING IN SEARCHING AND CUTTING AND PASTING TECHNIQUES. NOTED THAT DR. YSERN INDICATED HE IS APPROXIMATELY 80% THROUGH THE CHEMISTRY REVIEW, WHICH IS TARGETED FOR MARCH COMPLETION AND THERE ARE NO MAJOR ISSUES IN THE REVIEW TO DATE. \\ CHILD

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SUB	AVANDIA	NDA-21071	02/18/1999	AMENDMENT TO PENDING APPLICATION	SUBMITTED, IN RESPONSE TO THE FDA"S 2/2/1999 REQUEST, ADDITIONAL DISSOLUTION AND METHOD VALIDATION DATA. NOTED THAT SB SUBMITTED TWO REPLACEMENT FIGURES FOR NDA ITEM 6B.7, FOUND IN VOLUME 1.6.001, PAGES 38 AND 40. ALSO NOTED THAT SB ALSO SUBMITTED SEVEN VALIDATION REPORTS THAT SUPPORT CLINICAL STUDIES 034, 035, 031, 036, 064, 039 AND 049: GENERAL/RSD-100SDL/1; BP-1002/DIGOXIN/1; BP-1003/DIGOXIN/1; BF-1007/SB-205312/1; BRL-049653/RSD-1005R1/1; BRL-049653/RSD-100R30/1; AND THE SCINTILLATION COUNTING VALIDATION FOR STUDY 049.
SUB	AVANDIA	NDA-21071	02/18/1999		SB PROVIDED THE TITLE AND LOCATION OF REPORT BRL-049653/RSD-100NPK/1.
SUB	AVANDIA	IND-43468-S-193	02/19/1999	INFORMATION AMENDMENT - CHEMISTRY/MICROBIOLOGY PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-117, AND DOCUMENTATION FOR ONE NEW INVESTIGATOR, JONATHAN C. FOX. ALSO SUBMITTED CMC INFORMATION FOR THREE 8 MG TABLET FORMULATIONS OF BRL-49653, COATED WITH THREE DISTINCT FILM COATS.
SUB	AVANDIA	NDA-21071	02/22/1999	AMENDMENT TO PENDING APPLICATION	SUBMITTED, IN RESPONSE TO THE FDA"S 2/11/1999 REQUEST, A COMPLETE COPY OF THE DATA, CONTROL STREAMS AND OUTPUTS OF THE NONMEM OUTPUT FILES FOR POPULATION PHARMACOKINETIC REPORT BRL-049653/RSD-100T7L/1.
CFF	AVANDIA	NDA-21071	02/23/1999		(FAX) FDA PROVIDED THEIR MINUTES FROM THE 1/20/1999 MEETING IN WHICH THE FILEABLITY, PRIORITY REVIEW STATUS AND THE NEED FOR AN ADVISORY COMMITTEE FOR AVANDIA WERE DISCUSSED.
MEMO	AVANDIA	NDA-21071	02/23/1999		DOCUMENTS A CONVERSATION BETWEEN CLARE KAHN AND MATT WHITMAN OF SB AND THE FDA IN WHICH SB INQUIRED AS TO WHETHER THE SALT DESIGNATION, "MALEATE" NEEDS TO BE USED IN PROMOTIONAL LABELING. NOTED THAT FDA ESTIMATED A TWO TO THREE WEEK REVIEW TIME FRAME FOR PROMOTIONAL PIECES.
CFF	AVANDIA	NDA-21071	02/23/1999		(FAX) FDA PROVIDED THE BIOPHARMACEUTICS REVIEWER"S COMMENTS ON STUDIES PN-011 AND PN-020.
SUB	AVANDIA	NDA-21071	02/24/1999		(FAX) SUBMITTED JUSTIFICATION OF DOSE LEVEL SELECTION IN THE RAT AND MOUSE CARCINOGENICITY STUDIES. ALSO SUBMITTED A TABLE OF ROSIGLITAZONE EFFECTS ON PATHOLOGY IN THE 2-YEAR RAT CARCINOGENICITY STUDY.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	NDA-21071	02/24/1999		(FAX) SB PROVIDED INFORMATION CONCERNING ROSIGLITAZONE METABOLITES IN RAT, DOG AND MAN. NOTED THAT THE POTENCY OF ONE OF THE ROSIGLITAZONE METABOLITES, SB-280789 (METABOITE 7) WAS INCORRECTLY STATED AS 1.6-FOLD LESS POTENT AND THE CORRECT VALUE IS 13.6-FOLD LESS POTENT.
SUB	AVANDIA	IND-43468-S-194	02/24/1999	OTHER PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR TWO NEW INVESTIGATORS, GERSTREIN AND ROWE, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-044, AND ELEVEN NEW INVESTIGATORS, BOWLING, COLE, DELCHER, EARL, GROCH, HYMAN, HERRON, HSI, KAPLAN, WARREN AND WEISS, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-133. ALSO SUBMITTED REVISED DOCUMENTATION FOR INVESTIGATORS PREVIOUSLY SUBMITTED UNDER PN-008, PN-011, PN-024, PN-080, PN-082, PN-084, PN-093, PN-094, PN-095, PN-105, PN-114 AND PN-127.
SUB	AVANDIA	NDA-21071	03/02/1999		(FAX) SB, IN RESPONSE TO THE FDA"S 2/23/1999 REQUEST, PROVIDED A COPY OF DATA SET PLOTS FOR STUDIES PN-011 AND PN-020. NOTED THAT A COPY OF THIS EXACT FACSIMILE WAS MAILED TO THE FDA WITH A DISKETTE.
MEMO	AVANDIA	NDA-21071	03/02/1999		DOCUMENTS A CONVERSATION IN WHICH THE FDA COMMENTED THAT SB"S TOXIC DOSES WERE NOT IDEALLY SPACED ON TERMS OF DOSE INCREMENT AND REQUESTED THAT THE MINIMUM TOXIC DOSE BE CALCULATED BY BACK-EXTRAPOLATION OF SB"S AVAILABLE DATA FOR ATRIAL THROMBOSIS, HYDROTHORAX, CARDIAC HYPERTROPHY AND LIVER EFFECTS.
SUB	AVANDIA	NDA-21071	03/04/1999		(FAX) SB REQUESTED REVIEW OF THE AVANDIA TRADEMARK AT THE NEXT NOMENCLATURE COMMITTEE MEETING ON 3/23/1999.
SUB	AVANDIA	NDA-21071	03/04/1999		(FAX) PROVIDED A COPY OF THE 3/4/1999 FACSIMILE IN WHICH SB REQUESTED REVIEW OF THE AVANDIA TRADEMARK AT THE NEXT NOMENCLATURE COMMITTEE MEETING ON 3/23/1999.
SUB	AVANDIA	IND-43468-S-196	03/05/1999	PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-134, AND DOCUMENTATION FOR ONE NEW INVESTIGATOR, DR. J. GARY EVANS.
SUB	AVANDIA	IND-43468-S-195	03/05/1999	SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-1998009607-1, INITIALLY SUBMITTED ON 4/24/1998.
SUB	AVANDIA	IND-43468-S-197	03/11/1999	RESPONSE TO FDA REQUEST	SUBMITTED SB"S RESPONSE TO THE FDA"S 1/4/1999 BIOPHARMACEUTICS COMMENTS AND QUESTIONS REGARDING THE 0.5 HOUR TRIAZOLAM BLOOD SAMPLE ON DAY 14 FOR STUDY 116 AND THE QUALIFICATIONS OF THE PRIMARY INVESTIGATOR FOR STUDY 116, DR. JONATHAN FOX.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	NDA-21071	03/12/1999		SB REQUESTED PRE-CLEARANCE BY DDMAC OF THE PROPOSED LOGO AND SAMPLE CARTONS. // PARENT
SUB	AVANDIA	NDA-21071	03/12/1999	OM PSC	SUBMITTED LOGO WITHOUT ICON, LOGO WITH ICON, SAMPLE CARTONS WITHOUT ICON 315862, 315961 AND 316061, SAMPLE CARTONS WITH ICON 315862, 315961 AND 316061. 2 MG 60 TILTAB TABLETS SAMPLE 315866 AND 4 MG 30 TILTAB TABLETS SAMPLE 315967, BASED ON DRAFT LABELING AV:L1. // CHILD
SUB	AVANDIA	NDA-21071	03/15/1999		(FAX) SUBMITTED INFORMATION REGARDING THE CALCULATION OF MINIMUM TOXIC DOSES AND CORRESPONDING AUC"S FOR SELECTED TOXICITY PARAMETERS IN KEY REGULATORY STUDIES CONDUCTED WITH ROSIGLITAZONE MALEATE. NOTED THAT SB INFORMED THE FDA OF A CORRECTION TO TABLE 3 OF ITEM 3E.
MEMO	AVANDIA	NDA-21071	03/16/1999		DOCUMENTS A CONVERSATION IN WHICH DR. YSERN INFORMED SB THAT THE FDA NOMENCLATURE REVIEW COMMITTEE HAS REVIEWED AND APPROVED THE TRADENAME, AVANDIA, WITHOUT ANY OBJECTION. NOTED THAT DR. YSERN ALSO MENTIONED THAT THE CHEMISTRY REVIEW IS COMPLETE AND SB SHOULD BE RECEIVING THE LIST OF QUESTIONS OR COMMENTS NEXT WEEK.
SUB	AVANDIA	IND-43468-S-198	03/17/1999	INFORMATION AMENDMENT - CHEMISTRY/MICROBIOLOGY PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-108, AND DOCUMENTATION FOR ONE NEW INVESTIGATOR, RICHARD REYNERTSON, WHO WILL CONDUCT A STUDY IN ACCORDANCE WITH PN-108. ALSO SUBMITTED CHEMISTRY, MANUFACTURING AND CONTROL (CMC) INFORMATION FOR 10 MG AND 20 MG CAPSULES CONTAINING ATORVASTATIN CALCIUM TABLETS (FORMULA CODES AB AND AA, RESPECTIVELY) AND A MATCHING PLACEBO CAPSULE (FORMULA CODE SR).
SUB	AVANDIA	NDA-21071	03/18/1999	AMENDMENT TO PENDING APPLICATION	SUBMITTED, IN RESPONSE TO AN FDA REQUEST, COPIES OF THE 2/24/1999 AND 3/15/1999 FACSIMILES, WHICH RESPONDED TO QUESTIONS DR. HERMAN RHEE OF THE FDA RAISED DURING THE 2/11/1999 FDA MEETING FOR ELECTRONIC NDA TRAINING.
SUB	AVANDIA	NDA-21071	03/18/1999	AMENDMENT TO PENDING APPLICATION	SUBMITTED A COPY OF THE 3/2/1999 FACSIMILE AND DISKETTE SENT TO DR. MICHAEL FOSSLER OF THE FDA.
SUB	AVANDIA	IND-43468-S-199	03/18/1999	SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-1998030137-1, INITIALLY SUBMITTED ON 12/29/1998.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-200	03/24/1999	OTHER PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR FIVE NEW INVESTIGATORS, DOYLE, FISH, MECKENLENBURG, ROSENSTOCK AND SALVATORE, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-133, AND FOURTY-FOUR NEW INVESTIGATORS, AZORR, BLEVINS, BLOCK, BOWLING, DEBOLD, DEBRUIN, DEGRAFF, DOYLE, FIORILLO, FISHMAN, GARLAND, GILDERMAN, GROCH, HYMAN, HARPER, HERRON, KAYE, LITTLEJOHN, LOCHNER, MILLER, MORIN, NUNEZ, PATRON, PAHLE, PASTER, QUIGLEY, RENDELL, RIKALO, ROJAS, ROSENBLATT, ROSENSTOCK, RUBINO, SANT RAM, SCHWARTZ, SHARP, SMITH, STERNER, STONE, STONESIFER, TONKON, TOTH, WEERSAINGHE, WEINSTEIN AND ZIEVE, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-134. ALSO SUBMITTED REVISED DOCUMENTATION FOR INVESTIGATORS PREVIOUSLY SUBMITTED UNDER PN-080, PN-097, PN-105, PN-114, PN-127, PN-133 AND PN-134.
SUB	AVANDIA	IND-43468-S-201	03/24/1999	SAFETY REPORT - FOLLOW-UP	SUBMITTED FOLLOW-UP INFORMATION TO SAFETY REPORT, AE-1998030137-1, INITIALLY SUBMITTED ON 12/29/1998.
CFF	AVANDIA	NDA-21071	03/30/1999		FDA INFORMED SB THAT THEY HAVE CONCLUDED THAT NDA-21071 SHOULD RECEIVE A PRIORITY REVIEW. NOTED THAT THE USER FEE GOAL DATE IS 5/25/1999.
SUB	AVANDIA	NDA-21071	03/31/1999	AMENDMENT TO PENDING APPLICATION	SUBMITTED THE 120-DAY SAFETY UPDATE REPORT. NOTED THAT THE CLINICAL CUT-OFF DATE IS 11/7/1998.
SUB	AVANDIA	NDA-21071	03/31/1999		SUBMITTED THE BRIEFING DOCUMENT FOR THE 4/22/1999 ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEETING WHICH WILL DISCUSS THE SAFETY AND EFFICACY OF AVANDIA FOR THE TREATMENT OF HYPERGLYCEMIA IN TYPE 2 DIABETES MELLITUS, AS MONOTHERAPY AND IN COMBINATION WITH METFORMIN.
SUB	AVANDIA	NDA-21071	04/02/1999	AMENDMENT TO PENDING APPLICATION	SUBMITTED THE DRAFT SAMPLE CARTONS AND THE CORRESPONDING FOILS. NOTED THAT IT WAS NOT CLEAR IF THESE ITEMS, PREVIOUSLY SUBMITTED ON 3/12/1999, WERE EVER RECEIVED BY THE DIVISION.
CFF	AVANDIA	NDA-21071	04/06/1999		(FAX) FDA REQUESTED THAT SB FILL IN DATA ON MINIMUM TOXIC DOSE IN PRECLINICAL STUDIES FOR THE ADVERSE EVENTS, CARDIAC HYPERTROPHY, HYDROTHORAX, HEPATIC HYPERTROPHY, ATRIAL THROMBOSIS AND ALT INCREASE.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	NDA-21071	04/07/1999	AMENDMENT TO PENDING APPLICATION	SB PROVIDED DOCUMENTATION TO SUPPORT THEIR CONTENTION THAT PROTOCOL PN-011 WAS CONDUCTED IN A MANNER SUCH THAT THE RIGHTS AND SAFETY OF HUMAN SUBJECTS WERE ADEQUATELY PROTECTED. NOTED THAT ESTABLISHMENT INFORMATION AND INVESTIGATOR DOCUMENTATION IS PROVIDED.
MEMO	AVANDIA	NDA-21071	04/07/1999		DOCUMENTS A TELECONFERENCE BETWEEN DALE STOCKBOWER, SHARON SHAPOWAL AND MATT WHITMAN OF SB AND THE FDA IN WHICH DR. YSERN NOTED THAT, ALTHOUGH HIS CHEMISTRY REVIEW IS COMPLETE AND AWAITING SIGN-OFF, HIS COMMENTS ON THE SAMPLE LABELING MUST BE CONSIDERED UNOFFICIAL. DR. YSERN NOTED THAT HE HAS NO OBJECTIONS TO THE LOGO BUT MADE THREE RECOMMENDATIONS TO THE LABELING: DO NOT USE THE TILTAB PROPRIETARY NAME IN THE COMMERCIAL LABEL; USE FDA DRAFT GUIDANCE WORDING FOR STORAGE CONDITIONS; AND MODIFY THE 2MG AND 4MG SAMPLE COLOR BANDS, AS THEY ARE TOO SIMILAR AND MAY CAUSE CONFUSION.
CFF	AVANDIA	NDA-21071	04/09/1999		(FAX) FDA PROVIDED A COPY OF THE 12/1/1998 CORRESPONDENCE IN WHICH THE FDA AKNOWLEDGED RECEIPT ON 11/25/1998 OF SB"S 11/24/1998 NEW DRUG APPLICATION, ASSIGNED APPLICATION NUMBER NDA-21071 AND ASSIGNED THE THERAPEUTIC CLASSIFICATION OF STANDARD.
SUB	AVANDIA	NDA-21071	04/12/1999	AMENDMENT TO PENDING APPLICATION	SUBMITTED DRAFT CARTON AND SAMPLE LABELS WHICH INCORPORATE COMMENTS MADE BY DR. YSERN OF THE FDA ON 4/9/1999.
SUB	AVANDIA	IND-43468-S-202	04/13/1999	PROTOCOL AMENDMENT - NEW INVESTIGATOR PROTOCOL AMENDMENT - NEW PROTOCOL	SUBMITTED A NEW PROTOCOL, PN-135, AND DOCUMENTATION FOR ONE NEW INVESTIGATOR, DR. FRANKLIN J. ZIEVE.
MEMO	AVANDIA	NDA-21071	04/13/1999		(ELECTRONIC) DOCUMENTS RECEIPT OF THE 4/13/1999 FASCIMILE IN WHICH THE FDA PROVIDED THEIR CMC REVIEW OF THE AVANDIA NDA SUBMISSION. NOTED THAT THE FDA PROVIDED THREE RECOMMENDATIONS AND REQUESTS FOR THE CARTON LABELS.
SUB	AVANDIA	NDA-21071	04/13/1999	AMENDMENT TO PENDING APPLICATION	SUBMITTED, IN RESPONSE TO THE FDA"S 4/9/1999 REQUEST, A COPY OF THE SAS COMMAND FILES AND THE ASCII DATASETS IN PAPER AND ON DISKETTE FOR STUDY PN-028.
SUB	AVANDIA	NDA-21071	04/13/1999		(FAX) PROVIDED SB"S SAFETY SLIDES FOR THE AVANDIA ADVISORY COMMITTEE MEETING.
SUB	AVANDIA	NDA-21071	04/13/1999		(FAX) PROVIDED A COPY OF THE DRAFT EFFICACY SLIDES FOR THE ADVISORY COMMITTEE MEETING.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
CFF	AVANDIA	NDA-21071	04/13/1999		(FAX) FDA PROVIDED COMMENTS AND REQUESTS ON THE CARTON LABEL.
MEMO	AVANDIA	NDA-21071	04/13/1999		PROVIDED A COPY OF THE 3/30/1999 CORRESPONDENCE IN WHICH THE FDA INFORMED SB THAT THEY HAVE CONCLUDED THAT NDA-21071 SHOULD RECEIVE A PRIORITY REVIEW.
SUB	AVANDIA	NDA-21071	04/13/1999	AMENDMENT TO PENDING APPLICATION	SUBMITTED A REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES UNTIL AFTER APPROVAL OF NDA-21071 FOR AVANDIA. NOTED THAT SB PLANS TO SUBMIT AN OUTLINE OF PLANNED PEDIATRIC STUDIES TO THE FDA, FOLLOWING MARKETING APPROVAL OF AVANDIA.
SUB	AVANDIA	GENERAL	04/14/1999		(FAX) FDA PROVIDED INFORMATION ON ROSIGLITAZONE TOXICOLOGY WHICH WILL BE THE BASIS OF DISCUSSION AT THE 4/15/1999 MEETING.
CFF	AVANDIA	NDA-21071	04/15/1999		FDA PROVIDED A BACKGROUND PACKAGE FOR THE 4/22/1999 ADVISORY COMMITTE MEETING FOR AVANDIA.
MEMO	AVANDIA	NDA-21071	04/16/1999		(FAX) KARLA SANTINO OF SB PROVIDED CLARE KAHN OF SB WITH A COPY OF THE FDA"S STATISTICAL REVIEW AND EVALUATION OF THE AVANDIA NDA SUBMISSION.
SUB	AVANDIA	NDA-21071	04/20/1999	AMENDMENT TO PENDING APPLICATION	SUBMITTED, IN RESPONSE TO THE FDA"S 4/16/1999 REQUEST, NARRATIVES FOR PATIENTS WHO DEMONSTRATED TRANSITIONS IN HEMATOLOGY TESTS FROM NORMAL OR F1 AT BASELINE TO F3 FLAGS.
SUB	AVANDIA	NDA-21071	04/20/1999		(FAX) SUBMITTED THE NARRATIVES FOR THE FOUR PATIENTS WITH SERIOUS ADVERSE EXPERIENCES OF ANEMIA, 011.012.00698, 020.720.01004, 024.030.02226 AND 084.004.70042.
CFF	AVANDIA	NDA-21071	04/20/1999		FDA PROVIDED THEIR DRAFT STATISTICAL REVIEW AND EVALUATION OF THE CLINICAL STUDIES IN THE AVANDIA NDA SUBMISISON.
MEMO	AVANDIA	NDA-21071	04/20/1999		(ELECTRONIC) DOCUMENTS A CONVERSATION BETWEEN PETER KITZ AND SHARON SHAPOWAL OF SB AND THE FDA IN WHICH SB EXPLAINED THAT THERE HAD BEEN A MISTAKE ON SB"S PART BY PUTTING THE NOTE "PROTECT FROM LIGHT" ON THE BLISTER (SAMPLE) CARTON LABELS. SB NOTED THAT THERE WAS NO DATA IN THE NDA TO SUGGEST THAT SUCH A STATEMENT WAS REQUIRED, AND SUCH LANGUAGE MIGHT CAUSE UNDUE CONCERN FOR THE CUSTOMERS. ALSO NOTED THAT SB PROPOSED TO USE FOR LAUNCH THE PRINTED SAMPLE CARTONS AND IMMEDIATELY AT THE NEXT PRINTING, REMOVE THE "PROTECT FROM LIGHT" TEXT.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	NDA-21071	04/20/1999		(FAX) PROVIDED THE FOLLOWING INFORMATION: THE TABULATION OF PATIENTS WITH ANY ON-THERAPY ALT > 2.5X BUT LESS THAN OR EQUAL TO 3X ULTT; REVISED NARRATIVES FOR PID 105.022.30245/024.030.03004 AND PID 024.032.02518; AND THE ADVISORY COMMITTEE MEETING OVERHEADS FOR SB.
SUB	AVANDIA	GENERAL	04/21/1999		(FAX) PROVIDED SEVEN PAGES WHICH CONSTITUTE THE ERRATA PAGES OF THE AVANDIA BRIEFING DOCUMENT.
MEMO	AVANDIA	NDA-21071	04/22/1999		PROVIDED A COPY OF SLIDES CONCERNING LIVER SAFETY USED AT THE 4/22/1999 ADVISORY COMMITTE MEETING.
MEMO	AVANDIA	NDA-21071	04/22/1999		FDA"S AGENDA AND OVERVIEW FOR THE 4/22/1999 AND 4/23/1999 ENDOCRINOLGIC AND METABOLIC DRUGS ADVISORY COMMITTEE.
SUB	AVANDIA	NDA-21071	04/28/1999	AMENDMENT TO PENDING APPLICATION	SB REQUESTED PERMISSION TO USE THE SAMPLE CARTIONS WHICH CONTAIN THE ERRONEOUS TEXT "PROTECT FROM LIGHT" FOR THE INITIAL LAUNCH AND TO DELETE THE TEXT "PROTECT FROM LIGHT" AT THE NEXT PRINTING. SB NOTED THAT THE IMMEDIATE CONTAINER LABELS HAVE NOT BEEN PRINTED AND WILL BE REVISED ACCORDINGLY. NOTED THAT OUTER CARTON LABELS FOR THE PATIENT TRIAL KITS ARE PROVIDED.
CFF	AVANDIA	NDA-21071	04/28/1999		DDMAC NOTED THAT SB"S PRESS RELEASE ENTITLED, "FDA ADVISORY COMMITTEE UNANIMOUSLY RECOMMENDS SMITHKLINE BEECHAM"S AVANDIA FOR TREATMENT OF TYPE 2 DIABETES" CONSTITUTED PRE-APPROVAL PROMOTION AND WAS IN VIOLATION OF 21 CFR 312.7. NOTED THAT FDA REQUESTED SB"S RESPONSE BY 5/12/1999.
SUB	AVANDIA	NDA-21071	04/29/1999		(FAX) PROVIDED REVISED PAGES FOR THE PACKAGE INSERT PERTAINING TO LIVER SAFETY ISSUES AND A STUDY OUTLINE FOR A UNITED STATES POST-MARKETING STUDY.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-203	05/03/1999	OTHER PROTOCOL AMENDMENT - NEW INVESTIGATOR	SUBMITTED DOCUMENTATION FOR TWENTY-FIVE NEW INVESTIGATORS, AZORR, BLOOMGARDEN, BRICKMAN, CAPUZZI, CONWAY, FELICETTA, GROCH, HYMAN, HAVLICEK, HERSHON, ISAACSOHN, KNOPP, LEICHTER, LIPETZ, MCALLISTER, MCKENNEY, NEUTAL, PRICE, RIKALO, SCHWARTZ, SELTMAN, SUWANNASRI, TANDRON, TOTH AND WINGERT, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-108; TWO NEW INVESTIGATORS, GOLDSTEIN AND TAM, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-133; THIRTY-ONE NEW INVESTIGATORS, BOWERING, BRUNE, BUSE, BUSICK, CATHCART, DECHERNEY, DOMURAT, FEINGLOS, GALLINA, GOLDSTEIN, GOTTESMAN, HIRSCH, HOLLANDER, HOPKINS, JAIN, LA CAVA, LACKNER, LEWIN, MENEGHINI, MEZITIS, PI-SUNYER, NADEAU, PRICE, REYNERTSON, RICHARDSON, ROSS, TANENBERG, TONKENS, TOPKIS, VINIK AND WYSHAM, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-134; AND TWENTY-SEVEN NEW INVESTIGATORS, ALWINE, BRAUN, DOYLE, EDGAR, EVANS, GROCH, HYMAN, HEATLEY, HORST, KAYE, KEILLER, LORBER, LUCAS, MCCLANAHAN, MCKENNEY, MICHLIN, NEUTEL, PHILLIPSON, ROSENBLATT, ROSENSTOCK, SCOTT, SNYDER, STEINBRENNER, STOTLER, VADAKEKALAM, WEISS AND WINKLE, WHO WILL CONDUCT STUDIES IN ACCORDANCE WITH PN-135. ALSO SUBMITTED REVISED DOCUMENTATION FOR INVESTIGATORS PREVIOUSLY SUBMITTED UNDER PN-024, PN-079, PN-080, PN-082, PN-084, PN-094, PN-095, PN-096, PN-105, PN-112, PN-113, PN-114, PN-127, PN-134 AND PN-135.
SUB	AVANDIA	NDA-21071	05/03/1999		(FAX) PROVIDED A CLEAN COPY FAX OF SB"S PROPOSED LABEL. SB NOTED THAT THEY WILL FOLLOW UP WITH THE "COMPARE" VERSION VERSUS THE NDA AND THE ANNOTATED VERSION.
SUB	AVANDIA	NDA-21071	05/04/1999		(FAX) PROVIDED A BRIEF REVIEW OF THE PROCEDURES PREFORMED BY SB CLINICAL LABS TO DETERMINE THE REFERENCE INTERVAL FOR ALT WITH SUPPORTING DOCUMENTATION.
MEMO	AVANDIA	NDA-21071	05/04/1999		DOCUMENTS SEVERAL CONVERSATIONS IN WHICH ROBERT MISBIN OF THE FDA CONFIRMED HIS REQUEST FOR A LONG-TERM SAFETY STUDY AS SB"S SOLE PHASE 4 COMMITMENT AND NOTED HIS DISPLEASURE WITH SB"S REVISED DRAFT LABELING. NOTED THAT DR. MISBIN REACTED NEGATIVELY TO SB"S INTENTIONS TO INCLUDE THE PN-011 DATA WHICH, IN HIS OPINION, WAS OBTAINED UNETHICALLY. ALSO NOTED THAT DR. MISBIN DECLINED FURTHER DISCUSSION UNTIL AFTER THE 5/6/1999 FDA INTERNAL MEETING.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
MEMO	AVANDIA	NDA-21071	05/05/1999		(ELECTRONIC) DOCUMENTS A TELECONFERENCE BETWEEN SHARON SHAPOWAL AND RITA PATWARDHAN OF SB AND THE FDA IN WHICH THE FDA REQUESTED SB"S REASON FOR CHOOSING STUDY PN-020 FOR LIPIDS ADN INQUIRED ABOUT THE AMOUNT OF INCREASE IN LDL AND LDL/HDL RATIO WITH BOTH THE SUBGROUPS FOR THE MONOTHERAPY POOLED ANALYSIS.
MEMO	AVANDIA	NDA-21071	05/05/1999		(ELECTRONIC) DOCUMENTS A CONVERSATION BETWEEN MATT WHITMAN AND DALE STOCKBOWER OF SB AND THE FDA IN WHICH THE FDA AGREED THAT SB HAS ADEQUATELY DEMONSTRATED THE BIOEQUIVALENCE OF PHASE 3 TO COMMERCIAL TABLETS FOR ALL STRENGTHS OF AVANDIA TABLETS (1 MG, 2 MG, 4 MG, 8 MG). NOTED THAT FDA HAS CONCERN ABOUT USE, AND PATIENT SWITCHES FROM 2 MG BID TO 4 MG UID, AND THEREFORE REQUESTED THAT ADDITIONAL DISSOLUTION DATA, PER SUPAC-IR LEVEL 2 COMPOSITION CHANGE REQUIREMENTS, COMPARING THE COMMERCIAL 2 MG TABLET TO THE COMMERCIAL 4 MG TABLET. ALSO NOTED THAT SB CLARIFIED THAT BOTH THE PHASE 3 TABLETS AND THE COMMERCIAL TABLETS ARE MADE USING WET GRANULATION PROCESSES.
SUB	AVANDIA	NDA-21071	05/05/1999		(FAX) SUMITTED REVISED ANNOTATED LABELING INCORPORATING CHANGES MADE AS A RESULT OF THE FDA"S MEDICAL AND STATISTICAL REVIEWS AND THE RECOMMENDATIONS OF THE METABOLISM AND ENDOCRINE ADVISORY COMMITTEE. ALSO SUBMITTED SB"S PROPOSED PHASE IV POST-MARKETING PLAN.
SUB	AVANDIA	NDA-21071	05/05/1999	PEP PLT POT	SUBMITTED POSTCARD AV0366, ISSUED 4/26/1999; POSTCARD AV0386, ISSUED 5/10/1999, POSTER AV0579, ISSUED 4/28/1999; AND EXHIBIT PANELS AV991LT-LTH AND AV991G-GB, ISSUED 4/22/1999, BASED ON DRAFT LABELING AV:L1.
SUB	AVANDIA	IND-43468-S-204	05/06/1999	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED TWO AMENDMENTS TO PROTOCOL PN-109 AND ONE MODIFICATION TO PROTOCOL PN-131. NOTED THAT DETAILED LISTINGS OF THE AMENDMENTS AND MODIFICATION AND A COMPLETE COPY OF THE REVISED PROTOCOLS ARE PROVIDED.
SUB	AVANDIA	NDA-21071	05/06/1999		(FAX) SUBMITTED, IN RESPONSE TO THE FDA"S 5/6/1999 VOICEMAIL MESSAGE, ADDITIONAL TABLES WHICH SUPPORT THE NEW LABELING STATEMENTS.
SUB	AVANDIA	NDA-21071	05/06/1999		(FAX) PROVIDED THE CURRENT INFORMATION ON PATIENT 009.465.00078. NOTED THAT A MEMO FROM THE EUROPEAN CLINICAL GROUP ON THE STATUS OF THE FOLLOW-UP ON THIS PATIENT IS ALSO ATTACHED.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
MEMO	AVANDIA	NDA-21071	05/07/1999		(ELECTRONIC) DISTRIBUTED A COPY OF THE 4/28/1999 DDMAC NOTICE OF VIOLATION LETTER IN WHICH DDMAC NOTED THAT SB"S PRESS RELEASE ENTITLED, "FDA ADVISORY COMMITTEE UNANIMOUSLY RECOMMENDS SMITHKLINE BEECHAM"S AVANDIA FOR TREATMENT OF TYPE 2 DIABETES" CONSTITUTED PRE-APPROVAL PROMOTION AND WAS IN VIOLATION OF 21 CFR 312.7. NOTED THAT FDA REQUESTED SB"S RESPONSE BY 5/12/1999.
SUB	AVANDIA	NDA-21071	05/07/1999	AMENDMENT TO PENDING APPLICATION	SUBMITTED, IN RESPONSE TO THE FDA"S 5/3/1999 REQUEST, DISSOLUTION INFORMATION IN PH 4 BUFFER, 0.1M HCL, WATER AND PH 7.5 BUFFER, WITH DATA PRESENTED IN TABULAR AND GRAPHIC FORMATS AND WITH F2 CALCULATIONS. NOTED THAT SB COMMITTED THAT THE COMMERCIAL AVANDIA TABLET WILL MEET THE FILED DRUG PRODUCT SPECIFICATIONS AND THAT NO CHANGES ARE PROPOSED TO THOSE SPECIFICATIONS.
SUB	AVANDIA	NDA-21071	05/07/1999		(FAX) PROVIDED DR. YSERN OF THE FDA WITH A COPY OF THE 5/7/1999 SUBMISSION IN WHICH SB SUBMITTED, IN RESPONSE TO THE FDA"S 5/3/1999 REQUEST, DISSOLUTION INFORMATION IN PH 4 BUFFER, 0.1M HCL, WATER AND PH 7.5 BUFFER, WITH DATA PRESENTED IN TABULAR AND GRAPHIC FORMATS AND WITH F2 CALCULATIONS. NOTED THAT SB COMMITTED THAT THE COMMERCIAL AVANDIA TABLET WILL MEET THE FILED DRUG PRODUCT SPECIFICATIONS AND THAT NO CHANGES ARE PROPOSED TO THOSE SPECIFICATIONS.
SUB	AVANDIA	NDA-21071	05/07/1999		(FAX) PROVIDED DR. SHORE OF THE FDA WITH A COPY OF THE 5/7/1999 SUBMISSION IN WHICH SB SUBMITTED, IN RESPONSE TO THE FDA"S 5/3/1999 REQUEST, DISSOLUTION INFORMATION IN PH 4 BUFFER, 0.1M HCL, WATER AND PH 7.5 BUFFER, WITH DATA PRESENTED IN TABULAR AND GRAPHIC FORMATS AND WITH F2 CALCULATIONS. NOTED THAT SB COMMITTED THAT THE COMMERCIAL AVANDIA TABLET WILL MEET THE FILED DRUG PRODUCT SPECIFICATIONS AND THAT NO CHANGES ARE PROPOSED TO THOSE SPECIFICATIONS.
CFF	AVANDIA	NDA-21071	05/10/1999		(FAX) FDA NOTED THAT THE OVERALL HUMAN PHARMACOKINETICS SECTION IS ACCEPTABLE AND PROVIDED PHARMACOKINETIC AND LABELING COMMENTS.
CFF	AVANDIA	NDA-21071	05/10/1999		(FAX) FDA PROVIDED LABELING COMMENTS FROM THE BIOPHARMACEUTICS REVIEWER.
CFF	AVANDIA	NDA-21071	05/11/1999		(FAX) FDA PROVIDED THEIR LABELING RECOMMENDATIONS FOR THE AVANDIA PACKAGE INSERT.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	NDA-21071	05/11/1999		SB, IN RESPONSE TO THE FDA"S 4/28/1999 NOTICE OF VIOLATION LETTER, INFORMED THE FDA THAT THE ISSUANCE OF THE VIOLATIVE PRESS RELEASE WAS A ONE TIME EVENT AND IS NOT CURRENTLY BEING USED. SB ALSO CONFIRMED THAT THERE ARE NO OTHER SIMILAR PRESS RELEASES CURRENTLY IN USE OR BEING DISTRIBUTED.
SUB	AVANDIA	NDA-21071	05/11/1999		(FAX) SB, IN RESPONSE TO THE FDA"S 4/28/1999 NOTICE OF VIOLATION LETTER, INFORMED THE FDA THAT THE ISSUANCE OF THE VIOLATIVE PRESS RELEASE WAS A ONE TIME EVENT AND IS NOT CURRENTLY BEING USED. SB ALSO CONFIRMED THAT THERE ARE NO OTHER SIMILAR PRESS RELEASES CURRENTLY IN USE OR BEING DISTRIBUTED.
CFF	AVANDIA	NDA-21071	05/11/1999		(FAX) FDA PROVIDED THEIR LABELING RECOMMENDATIONS FOR THE AVANDIA PACKAGE INSERT.
CFF	AVANDIA	NDA-21071	05/11/1999		(FAX) FDA PROVIDED THEIR LABELING RECOMMENDATINS FOR THE PACKAGE INSERT.
MEMO	AVANDIA	NDA-21071	05/12/1999		DOCUMENTS A CONVERSATION IN WHICH SB REQUESTED A USER FEE FOR THE AVANDIA NDA-2 SUBMISSION. NOTED THAT FDA ASSIGNED USER FEE ID-3725.
MEMO	AVANDIA	NDA-21071	05/13/1999		(ELECTRONIC) DISTRIBUTED A COPY OF THE 5/13/1999 FACSIMILE SENT TO THE FDA REGARDING THE LIPIDS SECTION OF THE PACKAGE INSERT FOR AVANDIA.
MEMO	AVANDIA	NDA-21071	05/13/1999		(ELECTRONIC) DISTRIBUTED A COPY OF THE 5/13/1999 FACSIMILE WHICH PROVIDED REVISED DRAFT LABELING.
MEMO	AVANDIA	NDA-21071	05/13/1999		(ELECTRONIC) DISTRIBUTED A COPY OF SB"S PHASE 4 COMMITMENTS THAT WERE FAXED TO THE FDA ON 5/13/1999 TO SUPPORT THE 5/14/1999 FDA MEETING.
SUB	AVANDIA	NDA-21071	05/13/1999		(FAX) SB PROVIDED THEIR PROPOSED PHASE 4 COMMITMENTS.
SUB	AVANDIA	NDA-21071	05/13/1999		(FAX) SUBMITTED DATA CONCERNING THE LIPID CHANGES SECTION IN THE AVANDIA LABELING.
SUB	AVANDIA	NDA-21071	05/13/1999		(FAX) PROVIDED A COPY OF THE LABELING MARKED WITH REVISIONS.
SUB	AVANDIA	NDA-21071	05/13/1999		(FAX) PROVIDED A CLEAN COPY OF THE LABELING.
SUB	AVANDIA	NDA-21071	05/13/1999		(FAX) PROVIDED, IN RESPONSE TO THE FDA"S REQUEST, THE PATHOLOGY REPORT FOR PATIENT 009.465.00078.
SUB	AVANDIA	NDA-21071	05/17/1999		(FAX) PROVIDED THE ADDITIONAL LIPID ANALYSIS FOR AVANDIA. SB NOTED THAT THEY WILL REDRAFT THE SECTION.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	GENERAL	05/18/1999		SB NOTED THAT THEY ACCEPT THE MAJORITY OF THE REVISIONS TO THE LABELING PROPOSED BY THE FDA BUT PROVIDED THEIR FEW REMAINING COMMENTS ON THE LABEL THEY WOULD LIKE TO DISCUSS ON 5/19/1999.
SUB	AVANDIA	GENERAL	05/19/1999		(FAX) PROVIDED, IN RESPSONE TO THE FDA"S 5/18/1999 REQUEST, TWO TABLES FOR ADVERSE EVENTS GREATER THAN OR EQUAL TO TWO PERCENT AND MEAN LIPID CHANGES.
CFF	AVANDIA	NDA-21071	05/19/1999		(FAX) FDA PROVIDED THE BIOPHARMACEUTICS COMMENTS ON THE PACKAGE INSERT. // ATTACHED ADVERSE EVENTS TABLE
CFF	AVANDIA	NDA-21071	05/19/1999		(FAX) FDA PROVIDED THEIR STATISTICIAN"S COMMENTS ON THE SUMMARY TABLE FOR LIPID CHANGES AND REQUESTED THAT SB MAKE VARIOUS CHANGES.
SUB	AVANDIA	GENERAL	05/20/1999		(FAX) SB RESENT THEIR 5/5/1999 AND 5/13/1999 PHASE 4 COMMITMENT PROPOSALS.
SUB	AVANDIA	GENERAL	05/20/1999		(FAX) SB PROVIDED THEIR REVISED LABELING WHICH INCORPORATES ALL COMMENTS CONTAINED IN THE FDA"S 5/20/1999 FACSIMILE. SB NOTED THAT THE LIVER MONITORING SECTION REMAINS UNCHANGED PENDING DISCUSSIONS WITH THE REVIEWERS AND DR. JOHN JENKINS. SB ALSO NOTED THAT THEY HAVE ADDED A SENTENCE THAT THE PATIENTS SWITCHED TO AVANDIA FROM MAXIMUM METFORMIN HAD INCREASES IN LDL AND VLDL.
CFF	AVANDIA	NDA-21071	05/20/1999		(FAX) FDA PROVIDED ADDITIONAL LABELING COMMENTS FROM DR. MISBIN AND JOY MELE OF THE FDA.
CFF	AVANDIA	NDA-21071	05/20/1999		(FAX) FDA PROVIDED SB WITH A COPY OF THEIR 5/20/1999 AND 5/17/1999 INTERNAL MEMOS REGARDING LABELING CHANGES AND MINUTES OF THE 4/13/1999 EXECUTIVE CARCINOGENICITY ASSESSMENT COMMITTEE (CAC) MEETING.
CFF	AVANDIA	NDA-21071	05/20/1999		DDMAC REVIEWED SB"S 5/11/1999 RESPONSE TO THE THEIR 4/28/1999 LETTER, WHICH OBJECTED TO A PRESS RELEASE FOR AVANDIA, AND NOTED THAT THEY FIND SB"S ACTIONS ACCEPTABLE.
CFF	AVANDIA	NDA-21071	05/20/1999		(FAX) DDMAC REVIEWED SB"S 5/11/1999 RESPONSE TO THE THEIR 4/28/1999 LETTER, WHICH OBJECTED TO A PRESS RELEASE FOR AVANDIA, AND NOTED THAT THEY FIND SB"S ACTIONS ACCEPTABLE.
SUB	AVANDIA	NDA-21071	05/21/1999		(FAX) SUBMITTED, IN RESPONSE TO THE FDA"S 5/21/1999 REQUEST, FINAL IMMEDIATE CONTAINER AND CARTON LABELS.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	NDA-21071	05/21/1999	AMENDMENT TO PENDING APPLICATION	SUBMITTED, IN RESPONSE TO THE FDA"S 5/21/1999 REQUEST, FINAL CONTAINER AND CARTON LABELS.
SUB	AVANDIA	GENERAL	05/21/1999		(FAX) SB PROVIDED THE REVISED LABEL WHICH INCLUDES THE BIOPHARM DIVISION"S 5/21/1999 REVISIONS.
SUB	AVANDIA	GENERAL	05/21/1999		(FAX) SB PROVIDED THE LAST CHANGE TO THE LABELING AND REQUESTED IF THEY NEED THE WEIGHT GAIN FOR THE 52-WEEK STUDY SPELLED OUT IN TWO PLACES (WEIGHT SECTION AND WITH THE STUDY).
CFF	AVANDIA	NDA-21071	05/21/1999		(FAX) FDA PROVIDED MARKED-UP DRAFT LABELING FOR AVANDIA.
CFF	AVANDIA	NDA-21071	05/21/1999		(FAX) FDA PROVIDED THER MARKED-UP DRAFT LABELING FOR AVANDIA. // 38 PAGES
CFF	AVANDIA	NDA-21071	05/21/1999		(FAX) FDA NOTED THAT THE DISTRIBUTION AND DRUG INTERACTIONS SECTIONS OF THE LABELING SUBMITTED ON 5/20/1999 NEEDS TO BE CHANGED. NOTED THAT FDA PROVIDED THEIR PROPOSAL FOR THE WORDING.
SUB	AVANDIA	GENERAL	05/24/1999		(FAX) PROVIDED THE LABEL VERSION REVISED FURTHER FOLLOWING DISCUSSIONS WITH DR. JENKINS OF THE FDA. NOTED THAT THE EXPOSURE MARGINS INCLUDED UNDER PRECLINICAL SECTIONS ARE NOT EXACTLY AS NOTED BY THE PRECLINICAL REVIEWERS.
SUB	AVANDIA	GENERAL	05/24/1999		(FAX) SB PROVIDED A MARKED UP VERSION OF THEIR "IMPAIRMENT OF FERTILITY" AND ANIMAL "TOXICOLOGY" SECTIONS OF THE LABELING AND NOTED THAT THEY HAVE RESOLVED THE ISSUE ON SAFETY PRECLINICAL MICE.
SUB	AVANDIA	NDA-21071	05/24/1999		(FAX) PROVIDED TWO CHANGED PAGES TO THE AVANDIA LABEL. NOTED THAT SB ALSO REQUESTED CONSIDERATION OF LIVER MONITORING AS FOLLOWS: MONTHLY FOR THREE TO FOUR MONTHS IN ALL PATIENTS TO ENSURE SAFETY UPON INITIATION OF THERAPY; AND QUARTERLY FOR THE BALANCE OF THE YEAR AND PERIODICALLY THEREAFTER.
SUB	AVANDIA	GENERAL	05/24/1999		(FAX) PROVIDED A COPY OF THE 5/24/1999 FACSIMILE SENT TO JENA WEBER OF THE FDA IN WHICH SB PROVIDED TWO CHANGED PAGES TO THE AVANDIA LABEL. NOTED THAT SB ALSO REQUESTED CONSIDERATION OF LIVER MONITORING AS FOLLOWS: MONTHLY FOR THREE TO FOUR MONTHS IN ALL PATIENTS TO ENSURE SAFETY UPON INITIATION OF THERAPY; AND QUARTERLY FOR THE BALANCE OF THE YEAR AND PERIODICALLY THEREAFTER.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	GENERAL	05/24/1999		(FAX) SB PROVIDED THE CURRENT VERSION OF THE DRAFT LABELING WHICH INCLUDES DR. JENKIN"S, THE BIOPHARM DIVISION"S AND PRECLINICAL"S INPUT.
CFF	AVANDIA	NDA-21071	05/24/1999		(FAX) FDA PROVIDED PHARMACOLOGY COMMENTS FOR THE FOLLOWING LABELING SECTIONS: CARCINOGENESIS, MTUAGENESIS, IMPAIRMENT OF FERTILITY; ANIMAL TOXICOLOGY; PREGNANCY AND NURSING MOTHERS.
CFF	AVANDIA	NDA-21071	05/24/1999		(FAX) FDA PROVIDED A REVISED VERSION OF THEIR PREVIOUS 5/24/1999 FACSIMILE IN WHICH THEY PROVIDED PHARMACOLOGY COMMENTS FOR THE FOLLOWING LABELING SECTIONS: CARCINOGENESIS, MTUAGENESIS, IMPAIRMENT OF FERTILITY; ANIMAL TOXICOLOGY; PREGNANCY AND NURSING MOTHERS.
SUB	AVANDIA	NDA-21071	05/24/1999		(FAX) FDA PROVIDED THE REVISED LABELING, AS REQUESTED BY JOHN JENKINS OF THE FDA. SB NOTED THAT ALL ITEMS WERE CHANGED EXCEPT FOR TWO ITEMS, WHICH ARE BEING CHECKED WITH PRECLINICAL SAFETY (LINES 542 AND 566).
SUB	AVANDIA	NDA-21071	05/25/1999		(FAX) PROVIDED A COPY OF THE DRAFT APPROVAL PRESS RELEASE AND THE 5/25/1999 SUBMISSION WHICH CONTAINS THE PHASE FOUR COMMITMENT LETTER.
SUB	AVANDIA	NDA-21071	05/25/1999		SUBMITTED SB"S COMMITMENT FOR A LONG-TERM PHASE FOUR SAFETY AND EFFICACY STUDY, "ADOPT."
SUB	AVANDIA	GENERAL	05/25/1999		(FAX) SB PROVIDED TWO CHANGES TO THE LABELING: DELETED THE SECOND OCCURRENCE OF THE TERM "REDUCED" IN LINE 564; AND CHANGED THE PERCENTAGE OF HYPOGLYCEMIA WITH GLYBURIDE FROM 12.7 PERCENT TO 12.1 PERCENT IN LINE 273.
SUB	AVANDIA	GENERAL	05/25/1999		(FAX) SB PROVIDED THE LAST FOUND TYPOS/INCONSISTENCIES IN THE LABEL. NOTED THAT THESE ERRORS HAVE BEEN CORRECTED ON THE DISKETTE OF LABELING THAT WILL BE HAND DELIVERED TO THE FDA ON 5/26/1999.
CFF	AVANDIA	NDA-21071	05/25/1999		THE UNITED STATES DEPARTMENT OF STATE LEGALIZED THE CERTIFICATE OF ANALYSIS FOR AVANDIA LOT X102-8BRL1 TO SAUDI ARABIA. // CONSULARIZED BY SAUDI ARABIA
CFF	AVANDIA	NDA-21071	05/25/1999		THE UNITED STATES DEPARTMENT OF STATE LEGALIZED THE CERTIFICATE OF ANALYSIS FOR LOT X132-8BRL8 TO THE HASHEMITE KINGDOM OF SAUDI ARABIA. // CONSULARIZED BY SAUDI ARABIA
CFF	AVANDIA	NDA-21071	05/25/1999		THE UNITED STATES DEPARTMENT OF STATE LEGALIZED THE CERTIFICATE OF COMPOSITION, SPECIFICATIONS AND FUNCTIONS OF EXCIPIENTS FOR AVANDIA TABLETS TO THE HASHEMITE KINGDOM OF SAUDI ARABIA. // CONSULARIZED BY SAUDI ARABIA

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
CFF	AVANDIA	NDA-21071	05/25/1999		THE UNITED STATES DEPARTMENT OF STATE LEGALIZED THE CERTIFICATE OF ANAYSIS FOR AVANDIA LOT X122-8BRL4 TO THE HASHEMITE KINGDOM OF SAUDI ARABIA. // CONSULARIZED BY SAUDI ARABIA
CFF	AVANDIA	NDA-21071	05/25/1999		THE UNITED STATES DEPARTMENT OF STATE LEGALIZED THE CERTIFICATE OF ANAYSIS FOR AVANDIA LOT X122-8BRL2 TO THE HASHEMITE KINGDOM OF SAUDI ARABIA. // CONSULARIZED BY SAUDI ARABIA
CFF	AVANDIA	NDA-21071	05/25/1999		FDA APPROVED SB"S 11/25/1998 NEW DRUG APPLICATION WHICH PROVIDES FOR THE USE OF AVANDIA AS AN ADJUNCT TO DIET AND EXERCISE TO IMPROVE GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AS MONOTHERAPY OR IN COMBINATION WITH METFORMIN.
SUB	AVANDIA	NDA-21071	05/26/1999		SB REQUESTED AN EXPEDITED PRE-CLEARANCE BY DDMAC OF TWO CORE LAUNCH PIECES WHICH CONTAIN THE PRINCIPAL SALES MESSAGES TO BE USED IN THE LAUNCH OF AVANDIA: PHYSICIAN ANNOUNCEMENT LETTER AV0218 AND LAUNCH SALES AID AV0534. NOTED THAT SUPPORTING REFERENCES FOR THE PROMOTIONAL MATERIALS ARE PROVIDED.
SUB	AVANDIA	NDA-21071	05/27/1999		SB REQUESTED FIFTY-TWO CERTIFICATES OF PHARMACEUTICAL PRODUCT FOR THE FOLLOWING FIFTY COUNTYIES: ARGENTINA, ARUBA, BAHRAIN, BANGLADESH, BRAZIL, CHILE, CHINA, COLOMBIA, COSTA RICA, CURACAO, CYPRUS, DOMINICAN REPUBLIC, ECUADOR, EGYPT, EL SALVADORE, GUATEMALA, HONDURAS, HONG KONG, INDIA, INDONESIA, JAMAICA, JORDAN, KENYA, KOREA, KUWAIT, LEBANON, LIBYA, MALAYSIA, MALTA, MAURITIUS, MOROCCO, NICARAGUA, OMAN, PAKISTAN, PANAMA, PERU, PHILIPPINES, QATAR, SAUDI ARABIA, SINGAPORE, SRI LANKA, TAIWAN, THAILAND, TRINIDAD/TOBAGO, TURKEY, UNITED ARAB EMIRATES (UAE), URUGUAY, VENEZUELA, VIETNAM AND YEMEN. NOTED THAT SB REQUESTED TWO CERTIFICATES FOR HONG KONG AND LIBYA.

DOC CAT	REPORT NAME	APP NUMBER	DATE ISSUED	SUBMISSION CONTENT	DESCRIPTION
SUB	AVANDIA	IND-43468-S-205	05/28/1999	PROTOCOL AMENDMENT - CHANGE IN PROTOCOL	SUBMITTED, TO PROTOCOL PN-133, AMENDMENT TWO WHICH PROVIDES FOR THE EXCLUSION OF PATIENTS FROM PROTOCOL PN-133 WHO WERE WITHDRAWN FROM PROTOCOL PN-127 AFTER RANDOMIZATION DUE TO LACK OF EFFICACY OR HYPERGLYCEMIA. NOTED THAT MINOR INCONSISTENCIES REGARDING LABORATORY ANALYSES, PROTOCOL OBJECTIVES, GLYBURIDE SUPPLY, PROTOCOL ISSUE DATES, TREATMENT OVERDOSE AND MEDICAL MONITOR"S TELEPHONE NUMBER HAVE BEEN CORRECTED. ALSO NOTED THAT SECTIONS WITH REGARD TO ECGS HAVE BEEN UPDATED TO REFLECT THE CHANGE IN HANDLING PROCEDURE.

Avandia

Background/Overview of Clinical Investigations

Overview of Controlled Clinical Trials

The clinical development of rosiglitazone maleate (BRL 49653C) as a new oral antihyperglycemic (antidiabetic) agent has taken place over a *five*-year period from 1993 to 1998. The important events in development are summarized in Table 1.

Table 1

Important Events in the Development of Rosiglitazone

Month	Year	Event
Aug	1988	Rosiglitazone (free base) synthesized and initially investigated by Beecham Research Laboratories in Great Burgh, United Kingdom
Oct	1992	Preclinical studies (pharmacology, toxicology, and metabolism) initiated with maleate salt
Sep	1993	US IND for oral rosiglitazone submitted (IND 43,468)
Oct	1993	First oral administration to man: US oral rosiglitazone clinical trials initiated (Phase 1)
May	1994	Clinical hold following occurrence of ventricular arrhythmia in 2 volunteers - Hold lifted after meeting with Division on May 12, 1994
Jan	1995	First introduction of rosiglitazone for type 2 diabetes mellitus
Jan	1996	First intravenous administration to man
Jul	1996	End of Phase 2 meeting with the Division
Apr	1998	Pre-NDA meeting with the Division
Nov	1998	NDA for rosiglitazone tablets to treat type 2 diabetes mellitus submitted
Apr	1999	120-day safety update to be submitted

The Rosiglitazone Clinical Development Program to explore the pharmacology, efficacy, and safety in the treatment of patients with type 2 diabetes mellitus began in November 1993 with the first administration to healthy volunteers. A US IND application for rosiglitazone was submitted in September 1993. Clinical

trials in patients with type 2 diabetes mellitus commenced in January 1995. At the time of database freeze for this application over 4200 patients with type 2 diabetes and over 500 volunteers had received rosiglitazone. An overview of all completed and ongoing clinical studies with rosiglitazone in the treatment of hyperglycemia in patients with type 2 diabetes mellitus is provided in Table 2.

Table 2

Overview of Trials in the Clinical Program

Clinical Pharmacology	
Absorption, Distribution, Metabolism, and Excretion Studies	
Placebo-controlled	Healthy volunteers - 001, 002, 016, 029
Uncontrolled	Healthy volunteers - 004, 005, 013, 028, 030, 049, 107
	Patient volunteers - 007, 038 (renal dysfunction), 008 (hepatic dysfunction)
Pharmacodynamic Studies in Patients	
Placebo-controlled	033, 043 (both studies currently ongoing)
Pharmacodynamic Effects Unrelated to Therapeutic Effect	
Placebo-controlled	Healthy volunteers - 078
Drug Interaction Studies	
Placebo-controlled	Healthy volunteers - 031 (oral contraceptives), 034 (digoxin), 035 (warfarin)
	Patients with Type 2 Diabetes - 014 (glyburide), 041 (ethanol)
Uncontrolled	Healthy volunteers - 036 (metformin), 037 (ranitidine), 039 (nifedipine), 040 (acarbose)
Phase 2/3 Program	
Monotherapy [Efficacy and Safety]	
Double-blind, parallel-group placebo-controlled	006, 011, 024. 090, 098
Double-blind, parallel-group active-controlled	020
Open-label active-controlled	080. 097
Long-term open-label uncontrolled	009, 084, 091, 105
Combination with Metformin [Efficacy and Safety]	
Double-blind, parallel-group, placebo-controlled	094
Double-blind, parallel-group, active controlled	093
Long-term open-label uncontrolled	113
Combination with Sulfonylurea [Safety]	
Double-blind, parallel-group placebo-controlled	015, 096
Double-blind, parallel-group active-controlled	079
Long-term open-label uncontrolled	112

see also 8.H.2.2, Figure 2.2

The worldwide Phase 2 and Phase 3 clinical trials program was designed to provide efficacy and safety data from adequate and well-controlled trials of rosiglitazone in the treatment of hyperglycemia in patients with type 2 diabetes mellitus. The program investigated rosiglitazone monotherapy as well as rosiglitazone in combination with other anti-diabetic agents. Efficacy results supporting the use of rosiglitazone as monotherapy or in combination with metformin are provided in this application. Combination therapy with sulfonylureas or with insulin will be submitted at a later date. The plan also explored both once daily and twice daily dosing regimens including a direct comparison of the two dosing regimens. Table 2 displays the 19 studies included in this submission; 13 of these studies support both efficacy and safety and 6 studies support safety alone.

Principal evidence of efficacy for **rosiglitazone monotherapy** is provided by the following two double-blind, placebo-controlled studies. Study **011** was a 26 week study of 533 patients at doses of 2mg, 4mg BD or placebo. Study **024** was a 26-week study in 959 patients at doses of 4mg, 8mg OD, 2mg, 4mg BD, or placebo.

The principal indices of efficacy in these studies was the effect of rosiglitazone on fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c), measured as the change from baseline to endpoint for all patients in the intent-to-treat population.

Additional efficacy data came from the following studies:

Study **020,** a 1 year active-controlled study in 598 patients at doses of 2mg, 4mg BD or glibenclamide

Study **006**, a 12 week placebo-controlled dose-ranging study in 350 patients at doses of 0.05mg, 0.25mg, 1mg, 2mg or placebo

Study **090**, an 8 week placebo-controlled dose-ranging study in 303 patients at doses of 2mg, 4mg, 6 mg BD or placebo

Study **098**, an 8 week placebo-controlled, dose-ranging study in 380 patients at doses of 4mg, 8mg, 12mg OD or placebo

Principal evidence of efficacy for **rosiglitazone in combination therapy with metformin** is provided by the following two double-blind studies. Study **094** was a 26 week study of 348 patients at doses of 4mg, 8mg OD or placebo [with background metformin], Study **093** was a 26 week study of 322 patients with treatments of 4mg BD rosiglitazone + metformin, 4mg BD rosiglitazone or metformin.

The principal indices of efficacy in these studies was the effect of rosiglitazone on fasting plasma glucose and glycosylated hemoglobin (HbA1c), measured as the change from baseline to endpoint for all patients in the intent-to-treat population.

Two cardiac safety studies were conducted to evaluate the effect of rosiglitazone on the structure and function of the heart using echocardiography. Study **080** evaluated rosiglitazone 4mg BD and glyburide in 203 patients and Study **097** evaluated rosiglitazone 8mg OD and glyburide in 234 patients.

In addition, three double-blind, placebo or active-controlled studies of **rosiglitazone in combination therapy with sulfonylureas** are included in support of safety. Study **015** was a 26 week study in 593 patients at doses of 1mg, 2mg BD or placebo [with background sulfonylurea]. Study **096** was a 26 week study in 347 patients at doses of 2mg, 4mg OD or placebo [with background sulfonylurea]. Study **079** was a 26 week study in 309 patients with treatments of 2mg BD rosiglitazone + sulfonylurea, 2mg BD rosiglitazone or sulfonylurea.

Long-term data were obtained in six open-label extension studies; 4 for rosiglitazone monotherapy (Study **009**, Study **084**, Study **091**, Study **105**), 1 for rosiglitazone in combination with metformin (Study **113**), and 2 for rosiglitazone in combination with sulfonylurea (Study **009**, Study **112**). The doses of rosiglitazone were 4mg BD or 8mg OD for monotherapy or combination with metformin; 2mg BD or 4mg OD for combination with sulfonylureas. Efficacy was a secondary objective and measured fasting plasma glucose and HbA1c.

Fourteen of the phase II/III studies were conducted in the U.S. (**006, 011, 024, 079, 080, 084, 090, 093, 094, 096, 097, 105, 112, 113**). The remaining five studies were conducted in Europe including the United Kingdom (**009, 015, 020, 091, 098**). All double-blind studies were completed at the time of the data cut-off of June 18, 1998, all open-label studies were ongoing.

Two major meetings were held with the Division during the course of development as follows:

- End of Phase 2 meeting of July 22, 1996, at which time feedback and agreement was reached on suitable plans for clinical development in Phase 3 (see attachment 1 to section 8.B). Please note that the briefing document for this meeting was submitted to **IND 43,468** on June 28, 1996 [Serial No. 050] and post-meeting minutes were submitted on August 29, 1996 [Serial No. 055].

- Pre-NDA meeting of April 30, 1998. The concluding phase 3 development plans and preliminary data were reviewed at this pre-NDA meeting, at which time the basis for the initial NDA content and the file format were agreed (see attachment 2 to section 8.B). Please note that supporting documentation was submitted to **IND 43,468** on April 16, 1998 [Serial No. 153] and April 22, 1998 [Serial No. 154] and post-meeting minutes on June 2, 1998 [Serial No. 160].

  Please note that SB has complied with the agreements made with The Division at the pre-NDA meeting with the exception that this initial NDA supports two indications (monotherapy and combined use with metformin) rather than a single indication for monotherapy as proposed. As a result, 5 pivotal efficacy trials are contained in the NDA encompassing both OD and/or BD dosing regimens. This filing strategy has since been deemed a suitable by The Division.

Rosiglitazone, a potent peroxisome proliferator-activated receptor-γ (PPARγ) agonist has been in clinical development since 1993 for the treatment of hyperglycemia in patients with type 2 diabetes mellitus. An extensive series of clinical pharmacology, efficacy and safety trials have been conducted in over 4300 patients and over 500 volunteers. This experience forms the basis for this NDA and supports the proposed labeling for the treatment of hyperglycemia of type 2 diabetes mellitus as monotherapy in patients who are inadequately controlled on diet and exercise and as combination therapy with metformin in patients who are inadequately controlled by metformin monotherapy.

End of Phase 2 Meeting Agreements

At the July 22, 1996 meeting to discuss BRL 49653C (rosiglitazone) for the treatment of patients with type 2 diabetes mellitus, the following items were agreed between SmithKline Beecham Pharmaceuticals (SB) and the FDA. [Statements in bold type indicate meeting agreements or recommendations. These are followed by SB's response to the agreement.]

- **FDA recommended that a repeat phase 2 dose-ranging study employing doses of 8 mg/day and higher be performed prior to commencing phase 3 trials. It was subsequently agreed that this study could be conducted in parallel with phase 3 studies and that doses in the range of 12 to 16 mg/day might be included in such a study of short-term duration. It was also suggested that SB consider exploring BD versus OD dosing in any further phase 2 dose-ranging study.**

Studies 090 and 098 have been added to the clinical program. Study 090, an 8 week, placebo-controlled, dose ranging (bd dosing) monotherapy study, was submitted on April 23, 1997 (Serial No. 083). Study 098 is similarly designed but doses are given once daily rather than twice daily. The study is being conducted in Europe as a non-IND study. Both of these studies have examined total daily doses of 4, 8 and 12 mg.

- **Based on efficacy demonstrated in phase 2 study 006 (0.4% decrease in HbA1c - change from placebo at 4 mg/day dose after 12 weeks), SB was informed that a very clean safety profile would be necessary to support a positive risk:benefit assessment, to compensate for this marginal efficacy.**

It was agreed that 2 mg bd was acceptable as an appropriate low dose for phase 3 monotherapy trials. One and two mg bd were accepted as appropriate doses for use in phase 3 combination trials.

Doses of 4 and 8 mg/day are being studied in phase 3 monotherapy studies. Doses of 2, 4 and 8 mg/day are being studied in combination therapy studies.

It should be noted that maximal effects on HbA1c, a secondary endpoint, were not expected in study 006, given the short duration of the study. SB anticipates that clinical trials of longer duration will show a greater effect on HbA1c.

- **The Division indicated that in addition to demonstrating comparable efficacy between BD and OD regimens, it would also be necessary to demonstrate**

comparable safety. The Division recommended that two additional arms be included in study 024 (2 mg BD vs. 4 mg OD) to provide a link to the 4 mg/day dose being used in monotherapy and combination efficacy trials. The Division also recommended that the dosing regimen intended for marketing, OD or BD, be used in all phase 3 monotherapy and combination studies.

Study 024, a 26 week, placebo-controlled monotherapy study, was submitted on December 3, 1996 (Serial No. 061). The protocol was modified to include the additional two arms recommended by the Agency. The protocol now contains the following rosiglitazone treatment groups: 4 mg od, 8 mg od, 2 mg bd, 4 mg bd.

SB has added several once daily dosing studies to the phase 3 program to demonstrate comparable safety between the once daily and twice daily dosing regimens. These studies include:

Study 096, a 26 week, placebo-controlled sulfonylurea combination study (background glyburide [≥10 mg/day] + rosiglitazone [2 mg od, 4 mg od] or placebo) was submitted on February 25, 1997 (Serial No. 073).

Study 094, a 26 week, placebo-controlled metformin combination study (background metformin [2.5 g/day] + rosiglitazone [4 mg od, 8 mg od] or placebo) was submitted on February 26, 1997 (Serial No. 074).

Study 095, a 26 week, placebo-controlled insulin combination study (background insulin [≥ 30 units as bd injections] + rosiglitazone [4 mg od, 8 mg od] or placebo) was submitted on June 10, 1997 (Serial No. 092).

- **The proposed monotherapy and sulfonylurea, metformin, and insulin combination therapy studies assessing effects on glycemic control were viewed as providing a "reasonable basis" for assessing efficacy; there were no specific recommendations regarding study methodology.**

In addition, the Agency recommended that SB investigate whether the effects of rosiglitazone are additive or synergistic when used in combination with another therapy (reference FDA telephone conversation 22 March 1996 - Ser. No. 046). SB added the following two studies to the clinical development program utilizing FDA recommended study designs to evaluate a possible synergistic effect:

Study 079, a 26 week, placebo-controlled sulfonylurea combination study (rosiglitazone 2 mg bd + glyburide 10 mg bd versus placebo + rosiglitazone 2 mg

bd or placebo + glyburide 10 mg bd), submitted February 25, 1997 (Serial No. 071).

Study 093, a 26 week, placebo-controlled metformin combination study (rosiglitazone 4 mg bd + metformin 2.5g/day versus placebo + rosiglitazone 4 mg bd or placebo + metformin 2.5g/day), submitted April 11, 1997 (Serial No. 080).

- **At the time of the End of Phase 2 Meeting, the Division was still assessing what criteria might be appropriate to support an "insulin rescue" claim, i.e. complete withdrawal of patients from insulin, and could not provide specific recommendations. SB was encouraged to submit a protocol for comment prior to initiating the study.**

SB has not yet finalized study plans to look at an "insulin rescue" claim, but will provide a draft protocol to the Agency prior to initiating such a study.

- **To support an "insulin sparing" claim, a substantial reduction in total insulin dose in patients receiving relatively large insulin doses would need to be demonstrated; a small reduction in a modest insulin dose (the example given was 30 units) would not likely support such a claim. It was suggested that the incidence of hypoglycemic episodes also be considered as a measure of benefit. However reduction in insulin dose frequency was not viewed favorably as a primary measure of efficacy.**

SB is conducting two combination studies with rosiglitazone added to insulin therapy:

Study 082, a 26 week, placebo-controlled insulin combination study (background insulin [≥ 30 units as bd injections] + rosiglitazone [2 mg bd, 4 mg bd] or placebo) was submitted on June 5, 1997 in Serial No. 090.

Study 095, a 26 week, placebo-controlled insulin combination study (background insulin [≥ 30 units as bd injections] + rosiglitazone [4 mg od, 8 mg od] or placebo) was submitted on June 10, 1997 in Serial No. 092.

These studies are intended to support the indication for use of rosiglitazone given once or twice daily as combination therapy with insulin for the reduction of hyperglycemia in the management of patients with insulin-requiring type 2 diabetes mellitus. The primary objective of each study is to evaluate the effectiveness of rosiglitazone in reducing hyperglycemia when administered to insulin-requiring type 2 diabetic patients who are inadequately controlled (i.e., fasting plasma glucose ≥ 140 mg/dL) on insulin alone. The primary efficacy endpoint of these studies is the change from baseline in

HbA1c after 26 weeks of treatment. Included in the secondary endpoints are the changes from baseline in total daily insulin dose and percent change in total daily insulin dose at week 26. Rosiglitazone/insulin combination groups will be compared with the insulin monotherapy group.

In patients using self-monitoring of blood glucose (SMBG) who achieve a mean capillary glucose of ≤ 100 mg/dL, the total daily insulin dose may be decreased by 20% to 30%, as often as needed after randomization. Insulin will be reduced for safety reasons only.

The incidence of hypoglycemia in the rosiglitazone/insulin combination groups and in the insulin monotherapy groups will be determined. In cases where symptoms suggestive of hypoglycemia are reported, efforts will be made to elicit if these are true episodes by taking a detailed history and checking the patient's diary card (which include SMBG) where appropriate. Data will be captured on the case report form as:

-number of times the patient reports an episode suggestive of hypoglycemia
-number of these episodes which were hypoglycemic episodes, in the opinion of the investigator

Adverse event reports of hypoglycemia will be grouped as follows:

-adverse event reports of hypoglycemia
-adverse event reports of hypoglycemia plus a plasma glucose of <50 mg/dL (glucose obtained at clinic visit)
-adverse event reports of hypoglycemia with third party intervention/hospitalization (if reported as a serious adverse event)

The frequency of these types of hypoglycemic events will be compared across the treatment groups as part of the safety assessment.

Patients experiencing recurrent hypoglycemic episodes (FPG < 50 mg/dL) may be withdrawn from the study altogether for safety reasons.

- **The proposed clinical safety database was considered adequate; however it was recommended that as much controlled (placebo or active) clinical experience beyond six months of treatment be obtained as possible, to better characterize the safety profile of the compound compared to the natural history of the disease.**

Studies are still ongoing. Therefore it is difficult to give a precise estimate of the exposure to rosiglitazone at the time of the initial NDA filing. However, it is estimated that approximately 3800 patients will have been exposed to rosiglitazone. Estimated exposure to rosiglitazone for ≥ 12 months by regimen is 740 patients bd and 160 patients od.

Of these patients, approximately 300 patients received rosiglitazone for one year in a double-blind, positive-controlled trial (study 020) and approximately 50 received rosiglitazone for one year in an open-label, positive-controlled study (study 080).

At the time of the 120 Day Safety Update (Nov. 1998 clinical cut-off), cumulative estimated exposure to rosiglitazone will be 4200 patients. Estimated exposure ≥ 12 months in duration is estimated to be 1100 patients bd and 500 patients od.

- **Cardiac hypertrophy and decreased hematocrit remain a concern from a risk perspective for the class; it was stated that data over a 5 to 10 year treatment period may be needed to totally dispel the left ventricular hypertrophy concern. The Division did not identify any safety concerns beyond cardiac hypertrophy and decreased hematocrit for this class.**

SB is conducting two monotherapy studies, one with once daily dosing and one with twice daily dosing with rosiglitazone to assess safety regarding cardiac hypertrophy.

Study 080, a 52+ week, open-label, positive-controlled study (rosiglitazone 4 mg bd or glyburide ≤ 20 mg/day) was submitted on September 24, 1996 in Serial No. 057.

Study 097, a 52+ week, open-label, positive-controlled study (rosiglitazone 8 mg od or glyburide ≤ 20 mg/day) was submitted on June 20, 1997 in Serial No. 094.

In these cardiac studies, M-Mode echocardiograms are performed at weeks 0, 12, 28, and 52. Interim analyses are planned for reviewing 6 month and 12 month data. Studies 080 and 097 will continue indefinitely, provided sufficient patients continue to participate. Interpretations of echocardiograms by reviewers with no knowledge of patient study group are made at a central site.

All phase 3 studies using rosiglitazone monitor hematologic parameters, including hemoglobin, hematocrit, platelet count, red cell count, MCV, MCH, MCHC, white cell count and differential. These safety parameters are monitored at baseline and at weeks 4, 8, 12, 18, 26, and every 3 months thereafter.

- **The relative incidence of hypoglycemia can be assessed in the phase 3 monotherapy and comparator studies, e.g., the head-to-head glibenclamide comparator study 020. FDA stressed the importance of pre-defining what symptoms will be coded as "hypoglycemic events" and suggested SB refer to the DCCT trial methodology in this regard. FDA recommended SB include 'naive', newly diagnosed, or 'average' diabetics as patients in this study rather than SU failures to provide a fairer comparison.**

Hypoglycemia is not expected to occur during monotherapy studies, as the mechanism of action of rosiglitazone does not lead to the stimulation of endogenous insulin production. In cases where symptoms suggestive of hypoglycemia are reported, a laboratory check of a random glucose measurement may be performed if deemed appropriate by the investigator. In the unlikely event of patients experiencing recurrent hypoglycemic episodes, the patient may be withdrawn from the study on safety grounds.

For all studies, reports of hypoglycemia will be grouped into:

-adverse event reports of hypoglycemia
-adverse event reports of hypoglycemia plus a plasma glucose of <50 mg/dL (glucose obtained at clinic visit)
-adverse event reports of hypoglycemia with third party intervention/hospitalization (if reported as a serious adverse event)

The frequency of these types of hypoglycemic events will be compared across the treatment groups as part of the safety assessment.

- **The statistical rationale proposed for analyzing comparable or superior efficacy in study 020 was accepted. The relative safety and efficacy profiles of two agents will be factored into assessment of any promotional claim for comparable (or superior) efficacy and for assessment of any comparator claim for (lack of) hypoglycemia. A confirmatory study may be required to support any promotional claims.**

SB acknowledges this point and will consult with the Agency if necessary.

- **FDA would be concerned with a lack of change in the overall HDL:LDL ratio if it is due to both HDL and LDL levels increasing, and such an effect would likely be reflected in the labeling.**

Phase 3 studies will be examining the cholesterol profile.

- **Weight change (gain) needs to be examined in the context of its effect on associated risk factors, mentioning blood pressure, insulin levels, and lipid profile as perhaps most important in this population. Dr. Troendle suggested analyzing collected weight data by stratifying it into subsets, e.g., 5% weight gain, 10% weight gain, etc. and correlating it with other risk factors. It would be useful to attempt to ascertain the underlying cause for any weight gain, e.g. fluid retention, increased or redistributed adipose tissue.**

The Integrated Summary of Safety plans to analyze weight as a % increase from baseline using the following divisors: ≥10 to <15, ≥15 to <20 and ≥20.

- **Fed/fasted study 004 would support a recommendation in the labeling that BRL 49653C may be taken without regard to food.**

  The final report of Protocol 004 (SB Report No. HP-1003/BRL049653/1) titled, "*Investigation of the Effect of Food on the Pharmacokinetics of BRL 49653C in Healthy Male Volunteers*" was submitted to the IND on June 9, 1995 (SN 029).

Summary of Pre-NDA Agreements

Priority Review/Filing Strategy:

- FDA cannot commit to a priority review until after the NDA is filed. The most likely scenario for a priority review would be based on a lack of hepatotoxicity in clinical trials. Lack of significant drug interactions and effectiveness in monotherapy would provide additional justification for a priority review.
- FDA recommended Filing Option 2 as the most expeditious route to a fast approval. This would consist of filing monotherapy data alone in the initial NDA with combination study results to be submitted in supplementary NDAs later on. However, the initial NDA will be required to include the entire patient safety database.
- The Rolling NDA concept is an innovative idea, but the Division cannot commit resources to reviewing study reports extensively ahead of an actual NDA submission. They are receptive to the idea of SB submitting reports to the IND primarily in an electronic and "NDA like" format.

Safety:

- SB will need to adequately address how increased LDL levels, increased weight, and reductions in hematocrit and hemoglobin factor into the overall risk to benefit equation for Avandia labeling.
- Cardiac safety experience in 080 and 097 was considered adequate to address cardiac safety issues although some concern was expressed about an IND safety report of Quinke's edema. It was also agreed that safety data from these ongoing studies did not need to be integrated in the initial ISS.
- The Division agreed in principle to SB's proposed liver enzyme testing of 3X, 5X, and 8X above normal in the safety analysis.

Labeling:

- Proposed labeling statements (starting dose of 4 mg/day in monotherapy or combination therapy; od or bd dosing; can be increased to 8 mg/day after 6-8 weeks) for efficacy and dosing were considered acceptable pending actual study outcomes. If Study 024 demonstrates bioequivalence between bd and od dosing, od dosing will be allowed in monotherapy without a confirmatory study.

- The proposed additional data analyses at the report level to support the monotherapy indication for use in drug naive patients and in previously treated patients was considered acceptable. The Division would not commit at this point as to whether labeling statements could be made based on these analyses; but it will be considered.
- As previously discussed with the Agency, 8 mg daily dosing in combination with sulfonylureas is acceptable in the absence of a specific study of this dose, assuming there is no dose-related safety issue.

Introduction:

The Avandia pre-NDA meeting was held April 30, 1998, with the FDA Division of Metabolism and Endocrine Products. SB participants included:

Rita Patwardhan	Biometrics
Robert Schriver	Biometrics
Martin Freed	Clinical Pharmacology
Jai Patel	Clinical R&D
Margaret Kreider	Clinical R&D
Elizabeth Rappaport	Clinical R&D
Michael Brennan	U.S. Regulatory Affairs
Clare Kahn	U.S. Regulatory Affairs
David Wheadon	U.S. Regulatory Affairs
Matthew Whitman	U.S. Regulatory Affairs
Hamish Ross	Project Management

FDA participants included:

Solomon Sobel	Division Director
Alexander Fleming	Medical Team Leader
John Gueriguian	Medical Reviewer
Michael Johnston	Project Manager
Jena Weber	Project Manager
Ronald Steigerwalt	Pharmacology Team Leader
Herman Rhee	Pharmacology Reviewer
Xavier Ysern	Chemistry Reviewer
Stephen Moore	Chemistry Team Leader
Hae Young Ahn	Biopharmaceutics Team Leader
Joy Mele	Biometrics Acting Team Leader

The meeting provided the basis for planning and proceeding with the planned Avandia NDA. Agreements and issues arising from the meeting are listed below and grouped by category.

Bases for Priority Review:

- Priority review would rest mainly on an excellent safety profile/ with no evidence of liver toxicity.

- "Superior" efficacy in monotherapy is highly desirable, however, consideration would be given to other agents currently available for monotherapy, e.g., SUs and metformin, not just troglitazone (which was a poor candidate for monotherapy).

- Lack of significant drug interactions is helpful but not a basis for priority on its own.

- FDA cannot commit to a priority review until after the NDA is filed.

Filing Strategy Option 1 versus Option 2

- There was a strong recommendation from the Medical Reviewers (Drs. Gueriguian and Fleming) to file Monotherapy first (option 2) and get to market as quickly as possible. This is the market niche indication. This would consist of filing monotherapy data alone in the initial NDA with combination study results to be submitted in supplementary NDAs later on.

- HOWEVER, following the meeting, Mike Johnston suggested that, before we consider switching our plans to Option 2, the Division should immediately discuss the staffing and anticipated workload for 4Q98/1Q99 (anticipated to be high) as there might be little difference between the Options if sufficient reviewers were not available to review multiple files even if we paid the extra user fees. He promised a more firm answer asap.

- In addition, ALL safety data from all indications must be submitted in the initial Integrated Safety Summary (ISS) so there may be little or no time/effort savings here. This should be considered as a favorably rapid option even if priority review is not assigned.

- 3 sNDAs would be filed for the remaining indications each with a User Fee. Priority for each would be assessed on individual merit versus marketed products.

- Once daily (OD) dosing in monotherapy will be adequately supported by the "monotherapy only file" with the condition that study 024 demonstrate

equivalence of od versus bd dosing such that "two" 26-week pivotal studies are available.

- The Rolling NDA concept is an innovative idea, but the Division cannot commit resources to reviewing study reports extensively ahead of an actual NDA submission. They are receptive to the idea of SB submitting reports to the IND primarily as electronic documents in an "NDA like" format.

Safety Issues:

- Overall safety experience and also cardiac safety experience from studies 080 and 097 was considered sufficient for filing and approval. It was also agreed that interim study reports from these two ongoing studies could be submitted as stand-alone entities referred to in the ISS but not necessarily integrated into the initial ISS if this saved some time up-front.

- SB will need to adequately address how increased LDL levels, increased weight, and reductions in hematocrit and hemoglobin factor into the overall risk to benefit equation for Avandia labeling.

- 3X, 5X and 8X elevations in LFTs were accepted as an appropriate means of monitoring for liver toxicity. Dr. Gueriguian recommended that test parameters be examined specifically in terms of the different types of toxicities they might represent.

- Dr. Gueriguian and Dr. Rhee both expressed some concern about an IND safety report of a case of Quinke's edema which was considered by the investigator to be possibly related to study medication. (This event occurred in non-IND extension study 091 in France.) SB agreed to provide additional details of this adverse experience to the Agency when the information becomes available.

- It was agreed that the second insulin combination use study (095) does not need to be integrated in the NDA file.

Response to 011 Data:

- There was a generally positive response to the profile of Avandia as presented in 011 data including the presentation of specifically Monotherapy efficacy data in 3 subsets:

- naive
- previous monotherapy
- previous multi therapy

- Safety need NOT be analyzed in these subsets as the description of the entire treated cohort was agreed to be the most conservative approach.

- Dr. Gueriguian noted the rise in LDL as a feature that would need to be fully addressed. The lipid changes were apparently not considered to be alarming but generally along the lines of those seen with troglitazone. The proposed additional analyses were deemed appropriate at the report and integrated summary level. He and Dr. Rhee both commented on the potential lack of triglyceride lowering as one feature that was less than appealing.

- In particular, Dr. Gueriguian stated the following:

  In his opinion, a rise in LDL of 10-15% could be regarded as clinically insignificant if one considered that a drop of 10-15% for a lipid lowering drug would be considered as conferring no benefit.

  Changes in hematological parameters must be fully explained. If hemodilution is playing a role, this should be demonstrated. Furthermore, the impact of hematological changes on the measurement of primary efficacy parameters should be investigated.

  A decrease in weight of 5% is considered clinically significant in the treatment of obesity according to the Metabolism & Endocrine Division's guidelines. Therefore, a 5% weight increase could be considered clinically significant. This will need to be addressed by SB.

Potential Labeling:

- Proposed labeling statements (starting dose of 4 mg/day in monotherapy or combination therapy; od or bd dosing; can be increased to 8 mg/day after 6-8 weeks) for efficacy and dosing were considered acceptable pending actual study outcomes. If Study 024 demonstrates bioequivalence between bd and od dosing, od dosing will be allowed in monotherapy without a confirmatory study.

- As previously discussed with the Agency, 8 mg daily dosing in combination with sulfonylureas is acceptable in the absence of a specific study of this dose,

assuming there is no dose-related safety issue (see question posed to the FDA in attachment 4).

- In order to secure labeling in monotherapy indicating use in previously treated as well as in diet/exercise-treated patients, it was deemed appropriate to analyze efficacy parameters in the three subsets as proposed, however, no guarantees were given that such labeling would be granted. N.B. Safety need NOT be analyzed in these subsets as the description of the entire treated cohort was agreed to be the most conservative approach.

- The Division concurred that Avandia's initial labeling should reflect the diagnosis of diabetes as 140 mg/dL as was the standard at the time the studies were conducted. In the future, the diabetic patient population will need to be defined by the new WHO and ADA standard of 126 mg/dL.

Data Analyses:

- It was generally agreed that graphs displaying primary efficacy parameters in the Intent-to-Treat (ITT) population would be adequate. For study report analysis plans, consideration of completers in addition to ITT and Efficacy Evaluable (EE) populations was recommended as necessary to understand the data appropriately.

- The Agency concurred with SB's proposal that those factors not defined by the statistical modeling analysis as being associated with lipid changes, warrant no further examination.

CANDA:

- A separate meeting/demonstration was requested. This Division is not yet adept at CANDA review. All necessary support was offered.

- It was agreed that paper copies of specified NDA volumes will be provided as reviewer's desk copies at the time of the NDA submission if requested in advance by the reviewer.

NDA Structure, Format and Content:

- It was agreed that efficacy data from Japanese studies and from ongoing studies need not be included in the efficacy summary. There were no comments on the proposed format or structure of the ISE.

- It was agreed that volunteer and patient clinical pharmacology safety data and data from Japanese studies need not be integrated with Phase II/III safety data. There were no comments on the proposed format or structure of the ISS.

- FDA agreed with SB's proposal to provide annotated CRF's for all patient deaths, serious adverse experiences, and withdrawals due to adverse experiences for randomized patients only and as electronic PDF files.

- FDA agreed with SB's proposal to provide patient narratives for deaths, serious adverse experiences, withdrawals due to adverse experiences (except for those related to progression of diabetes or lack of efficacy), and relevant laboratory findings of clinical concern for randomized patients on therapy only.

There were no comments on the proposed structure of the NDA Table of Contents.

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1	5,002,953	184	2100	----	07/457,272	03/26/91	12/27/89	08	NO	PAID

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